IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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IN RE BENDAMUSTINE CONSOLIDATED CASES) Civil Action No. 13-2046
) CONSOLIDATED

- - -

Wilmington, Delaware
Friday, December 4, 2015
9:00 a.m.
Trial Day 4

- - -

BEFORE: HONORABLE GREGORY M. SLEET, U.S.D.C.J.

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:18:09 **THE COURT: Good morning, counsel. Please, be**
:18:12 **seated.**
:18:14 **Let's pick up where we left off.**
:18:17 **Doctor, good morning.**
:18:18 **MR. SUNG: Good morning, Your Honor. May it**
:18:20 **please the Court...**
:18:20 **... PAUL JAROSZ, having been previously sworn as**
:18:20 **a witness, was examined and testified further as**
:18:20 **follows ...**
:18:22 **DIRECT EXAMINATION CONTINUED**
:18:22 **BY MR. SUNG:**
:18:23 Q. **Good morning, Dr. Jarosz. Welcome back.**
:18:25 A. **Good morning.**
:18:25 Q. **I would like to continue with our discussion from**
:18:28 **yesterday regarding the Maas publication. So that we are up**
:18:33 **to speed with the transition, was it your testimony**
:18:35 **yesterday that the Maas publication taught each and every**
:18:38 **limitation of Claim is 1, Claim 3 and Claim 5 of the '270**
:18:44 **patent either expressly or inherently?**
:18:47 A. **Yes.**
:18:47 Q. **If we can turn to your Tab 15, which is DTX-90.**
:18:58 **Dr. Jarosz, would you explain what this document**
:19:00 **is?**
:19:01 A. **This is Salmedix's initial IND, the Investigational**
:19:05 **New Drug Application. This specifically is a section on**

chemistry, manufacturing and control information.

Q. You have reviewed this document. Correct?

A. Yes, I have.

Q. Could you turn to Page 46 in that tab -- I know it's a rather long document -- to Section 7.2.13?

A. Yes.

Q. Have you reviewed this table before?

A. Yes, I have.

Q. Dr. Jarosz, can you describe what we see here?

A. This table is a summary of the photostability testing conducted by Salmedix on Ribomustin.

Q. Does it reference a particular lot number?

A. Yes. It references two lot numbers, and specifically, we will be focusing on 380800.

Q. Was data, to your recollection, reported elsewhere in this CMC report?

A. Yes.

Q. And if we can turn to, in that document, Page 150.

If we can blow up what you see in under the t equals 24 hours section.

Dr. Jarosz, are you familiar with this table?

A. Yes, I am.

Q. Can you describe for us what this table represents?

A. This table represents the photostability study that we just referenced. On the last page, the last illustration,

this is specifically the bendamustine 100 milligram lyophilate. And the column headings are Brown Glass Vial, Brown Glass Dark Control, Brown Glass Reference Standard, and then Clear Glass, the same vial, a dark control and a reference standard.

Q. Can you tell us what you see with respect to the data at the -- why don't you describe for us what t equals 24 represents?

A. Time, t, equals 24 hours. This is the 24-hour data point for this particular photostability study.

This light study, Your Honor, is just one where you put things in brown glass vials, clear glass vials, see what the result is going to be when one subjects it to a high illumination of light to see if there is any light degradation. One thing I would point out is that --

MR. WARE: Objection, Your Honor.

THE COURT: Basis.

MR. WARE: I don't think there is a question.

THE COURT: Okay. Fair enough.

BY MR. SUNG:

Q. Dr. Jarosz, can you describe, with respect to the t equals 24 hours, what the results that you see in these various columns represent?

A. So in the various columns, we have the principal decomposition products, BM1EE, HP1, HP2. In the brown

glass, dark control, what that means is the lyophilate was put into the brown glass vial and it was not subjected to any light. So this is the dark control.

In that column, the level of HP1 is 0.48.

Q. Mr. Vaughn, can we bring up DDX-31, please.

Do you recall your demonstrative slide from yesterday, Dr. Jarosz?

A. Yes, I do.

Q. Is the .48 measurement that we just saw with respect to the data, does that represent any one of these particular components that you see in the formula you have presented?

A. Yes. It represents the amounts of HP1 observed. That means that either the amount prior to the .48 observed value had to be something less, it certainly -- it could be either .48 or something less.

Q. Were you able to reach a conclusion with respect to the amount of HP1 vis-a-vis the patent claims?

A. Yes. That photostability study, that dark control, the photostability study, the .48 is certainly less than the limitation in Claim 1, about .9 percent. It certainly is less than the .5 percent in Claim 3. And at some point in time earlier, it could be less than the .4 percent limitation in Claim 5.

Q. Was the information about the amount of HP1 from that photostability study a matter of public record at the time

of the '270 patent?
A. It was not.
Q. You testified yesterday that you are aware of a number of other Ribomustin lot observed HP1 levels that were at different HP1 levels. Correct?
A. Correct.
Q. Does the data from other studies showing these higher amounts of HP1 in Ribomustin change your conclusion?
A. No.
Q. Why not?
A. Because this specific lot and this specific data point, at .48, certainly shows the existence of the amount of HP1 can be at least as low as .48.
Q. This was not a test or a study that you did. Is that correct?
A. That is correct. This is a Salmedix study.
Q. Did you address whether or not there might be a concern you cherry-picked that particular Ribomustin study showing a low HP1 amount?
A. Yes. I understand the concern could be that I cherry-picked. I didn't cherry-pick. I was looking for answering the question, are there any examples that show HP1 levels in the order of magnitude that the claims describe, about .9 percent, .5 percent, or .4 percent.
So the values of HP1 that are greater than .9 do

not allow me to answer the question, were there any values that were in the range of what the claim limitations are.

Q. Mr. Vaughn, can we go back to the Maas article, DTX-146, please.

That is in Tab 14 of your binder, Dr. Jarosz.

If we can go to the next-to-last page of this document. I am sorry. Page forward, please.

For the record, this is Page 13 of DTX-146.

Mr. Vaughn, can you go to the paragraph right above Section 4, experimental -- that's right. Do we have the English translation of this?

Dr. Jarosz, is the Tab 14 in your binder an English translation?

A. Yes, it is.

Q. While we are pulling it up on the screen, if you wouldn't mind, on Page 6 in what is your binder, there is a sentence right before Experimental Section, the last sentence of that paragraph in Section 3, Discussion.

A. Yes.

Q. Could you read that sentence for the record?

A. The last sentence states, "No stability issues are anticipated either for the recommended application as short-term infusion over 30 minutes since the bendamustine preparations remain stable over 9 hours at room temperature."

:29:04 Q. **Do you dispute that this is a teaching of the Maas article?**
:29:07 A. **It is one of the teachings of the Maas article.**
:29:07 Q. **Does this particular teaching change your conclusions with respect to Maas and its anticipatory effect?**
:29:11 A. **No.**
:29:14 **MR. SUNG: Your Honor, I wanted to see if we could revisit the issue with you of the Jeffrey Heckman e-mail.**
:29:17 **THE COURT: Yes.**
:29:22 **(The following took place at sidebar.)**
:29:25 **THE COURT: Okay.**
:29:27 **MR. SUNG: I didn't know if Mr. Ware wanted to renew his objection -- I guess with your ruling standing, I wanted to know what the basis of his objection was. Was it purely relevancy or was it evidentiary based on hearsay?**
:29:28 **MR. WARE: Your Honor, I have had a chance to look at this man's background. I am satisfied with respect to Rule 801(d)(2)(D) that your instinct is correct, that he falls within that. So my objection is not on that basis.**
:33:19 **However, I do object under Rule 403 for the reason that this has marginal relevance. It's unclear on the face of it.**
:33:19 **This appears to be an e-mail from a woman at Johnson & Johnson. We don't know for what reason. She may**
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be a competitor. He may be minimizing the differences for competitive reasons. We just don't know. But there was an opportunity to take discovery on this. It wasn't done. Multiple witnesses have been deposed over several years. It's also not clear whether he wrote the substantive part.

You will notice, it's detached below. He doesn't just roll into an explanation. He writes, you know, look below. And it may be that he simply attached something.

So while I can't dispute the fact that it's, quote, "intriguing," I am not sure it's more than intriguing.

On the other hand, I recognize that the Court is discerning and makes your own judgment. But my objection is on the basis of Rule 403 and the uncertainties around this, which could have been corrected in realtime during the course of discovery.

THE COURT: That's what concerns me, if you want to use a document like this. Is Mr. Heckman still in the employ? Still around? Was Heckman available to be deposed?

MR. WARE: Sure.

MR. SUNG: Your Honor, I can't speak to that portion of it in terms of whether we were able to take his deposition or not. What I can say, first of all, the e-mail was not from an external individual, Shirley Weisel. She is

responding to Mr. Heckman's e-mail to her. She basically says thanks up top in receipt of that.

So the information also doesn't have the indicia of anything other than a communication from a Cephalon employee to an individual at an outside organization.

I had heard yesterday that there was some concern over whether this was the type of information an expert would otherwise be relying upon.

THE COURT: I expressed that concern.

MR. SUNG: In the absence of it being hearsay and otherwise being admissible, Rule 703 does not preclude an expert from being able to rely on such information.

THE COURT: I will admit it. I will end up agreeing with you on this, that it's more a weight issue than an admissibility issue, given Mr. Ware's position, I think correctly stated, on the relevant hearsay rule.

That's all I will say about it.

I didn't mean to imply anything, other than just Sleet saying it was "intriguing." You shouldn't take anything, neither side, from that.

(End of sidebar conference.)

BY MR. SUNG:

Q. If you can turn to DTX-226, please. This is in Tab 4 of your binder, Dr. Jarosz.

You testified yesterday that you had referred to

this document as part of your consideration in this case?
A. Yes, I have.
Q. Can you remind us what this document represents?
A. This document is an e-mail --
MR. WARE: Object to that question, what it represents.
THE COURT: Yes. Sustained.
BY MR. SUNG:
Q. Dr. Jarosz, what is this document?
A. This document is an e-mail chain, starting with Jeffrey Heckman sending an e-mail to Shirley Weisel, part of J&J.
Q. And what was the date of this document, according to the e-mail header?
A. The e-mail from Jeffrey Heckman was November 10th, 2010.
Q. According to this e-mail, what is Jeff Heckman's role at Cephalon?
A. On the second page, his title is included. His title is director, project management.
Q. According to Mr. Heckman, on that same page, what conclusions did the FDA draw concerning Ribomustin and Treanda?
MR. WARE: Objection, Your Honor. The document is now in evidence. It speaks for itself.

:35:29 **THE COURT: I don't think this is necessary. I**
:35:30 **am going to sustain that.**
:35:35 **BY MR. SUNG:**
:35:36 Q. **If you go back to the first page, do you see in the**
:35:46 **first line whether or not there is a comparison between**
:35:52 **Treanda and Ribomustin?**
:36:04 A. **That third paragraph starts, "The two products are**
:36:09 **essentially the same."**
:36:11 Q. **Can you continue through that sentence, please?**
:36:15 A. **"...though the newer Treanda has been slightly**
:36:17 **modified to give a more pure and stable drug. Ribomustin**
:36:21 **has been made from bendamustine hydrochloride that meets all**
:36:25 **requirements but is less pure than that now used for**
:36:29 **Treanda."**
:36:30 Q. **Thank you. Can we turn to DTX-65, which is Tab 5 of**
:36:35 **your binder. Can you tell me what this document is?**
:36:45 A. **This is the investigator's brochure put together by**
:36:49 **Salmedix.**
:36:50 Q. **And what is an investigator's brochure?**
:36:52 A. **The investigator brochure is a scientific document**
:36:56 **that tells the investigators at the clinical trial known**
:37:00 **information about the compound.**
:37:01 Q. **If you could turn to Page 8 of that document. If I**
:37:10 **can refer you to the third paragraph. Could you read that**
:37:13 **into the record, the first sentence, please?**

A. **"Treanda has been marketed for almost 30 years in Germany, where it is known as Ribomustin (generic: bendamustine hydrochloride.)"**

MR. SUNG: Thank you, Dr. Jarosz. No further questions.

THE COURT: Thank you, Mr. Sung.

Mr. Ware, your witness.

CROSS-EXAMINATION

BY MR. WARE:

Q. **Good morning, Mr. Jarosz.**

A. **Good morning.**

Q. **Why don't we talk for a minute about the chemistry manufacturing control information which you discussed with us this morning, which I believe is DTX-90. Do you have that before you, sir?**

A. **Which tab is it?**

Q. **Pardon me?**

A. **Which tab is it?**

Q. **The exhibit is DTX-90. It is the document we have been talking about this morning -- it is 15, I am told.**

A. **Thank you.**

Q. **If I could direct you, sir, to Page 46, about which you were questioned a few moments ago, you indicated to us that in the section 7.2.13 on drug product photostability that the batch number on which you are relying for purposes**

of your discussion today is the 380800. Correct?
A. Correct.
Q. Now, that batch number is not a Thissen batch, is it?
A. I do not know.
Q. Well, it is not the same numbering system as the Thissen batches you referred us to yesterday in your direct examination, is it?
A. That is correct.
Q. In fact, it's consistent with batches from Thymoorgan or from Ribosepharm. Isn't that so?
A. For that number of digits, that is correct.
Q. So your understanding is that -- to the extent you drew any inference from this, you drew the inference that this was not a Thissen batch, and only Thissen batches and Pharmachemie batches were made available to Salmedix. Isn't that correct, so far as you know?
A. Well, I certainly know that the Thissen batches were made available, and I also know that this record says that they used this particular lot number, and this is a Salmedix study.
Q. So your inference is that Salmedix had this lot because this number appears in a document of theirs?
A. I understand this photostability study was conducted at Salmedix.
Q. Let's stick with the batches for a moment. Passing

:41:06 **whether it was or wasn't, it may have been conducted at**
:41:09 **Fujisawa. Isn't that correct?**
:41:13 A. **That is a possibility, yes.**
:41:14 Q. **You don't know one way or the other whether this was**
:41:17 **conducted by Fujisawa or by Salmedix. All you know is it's**
:41:22 **in an application filed with the Food and Drug**
:41:28 **Administration, even if the data came from Fujisawa.**
:41:30 **Correct?**
:41:51 A. **Yes. The data could have come from Fujisawa.**
:41:53 Q. **My point is simply -- we don't have to spend the**
:41:57 **morning on it -- you don't know where this particular lot**
:42:00 **came from, but you do know that it is inconsistent with the**
:42:04 **lot numbering system that you observed for Thissen batches.**
:42:08 **Isn't that correct?**
:42:10 A. **That is correct. It is a lot of Ribomustin.**
:42:13 Q. **All right. It's a lot of Ribomustin. But it's not**
:42:18 **Ribomustin so far as you know from anything you have read**
:42:20 **that was ever in the hands of Salmedix. Correct?**
:42:37 A. **I will acknowledge that this study could have been**
:42:39 **done at Fujisawa or it could have been done at Salmedix.**
:42:43 Q. **And you don't know which?**
:42:44 A. **That's correct.**
:42:45 Q. **Now, you also don't know whether this batch was ever**
:42:50 **sold in the United States. Isn't that so?**
:42:54 A. **That is so.**

:42:54 Q. **It may have been -- these studies may have been**
:42:58 **carried out by Fujisawa in Germany. Isn't that so?**
:43:01 A. **Yes.**
:43:01 Q. **We also have no information here with respect to how**
:43:09 **these batches were dissolved, do we, for purposes of the**
:43:14 **testing that you told us about?**
:43:17 A. **That is correct.**
:43:18 Q. **So we don't know the medium in which they were**
:43:21 **dissolved. It might have been methanol, it might have been**
:43:24 **acetonitrile. There is simply no information in this**
:43:29 **document with respect to that. Isn't that so?**
:43:37 A. **That is true.**
:43:38 Q. **Now, you will agree, would you not, that this is not**
:43:42 **the same batch that's used in the Maas reference to which**
:43:47 **you have spoken?**
:43:49 A. **That is correct.**
:43:49 Q. **Let me ask you, then, to turn to Page 150 of the**
:44:04 **document, Appendix 10, to which you referred this morning.**
:44:08 **Is that right?**
:44:09 A. **Yes, it is.**
:44:10 Q. **If we could highlight right at the top upper left in**
:44:15 **Column 2 where it says Brown Glass Dark Control. First of**
:44:22 **all, as I think you gave us a brief description, what is**
:44:30 **going on here is that UV radiation is bombing some of these**
:44:39 **samples. Isn't that right? And the purpose of that is to**

:44:42 **do accelerated stability study. Right?**
:44:44 A. **That is correct.**
:44:44 Q. **And one way of doing that is to put the Ribomustin**
:44:51 **cake in the vial in a container, some of which have clear**
:44:57 **glass, some of which have dark glass, opaque glass, and some**
:45:02 **of which of are just left out with no radiation at all.**
:45:05 **Isn't that right?**
:45:06 A. **That's correct.**
:45:06 Q. **And the object of the game is to test the**
:45:09 **decomposition or the increase or development of impurities**
:45:14 **over time?**
:45:16 A. **That's correct.**
:45:16 Q. **And rather than do that over six months or two months**
:45:19 **or a month, these acceleration studies can be done in 24**
:45:24 **hours, or all of the times we saw in the left-hand column,**
:45:29 **and they provide certain information. Isn't that so?**
:45:33 A. **That is true. This study actually ran to 72 hours.**
:45:38 Q. **So this one was three days.**
:45:40 **If we look in Column 4, in the clear glass vial,**
:45:47 **there are a bunch of numbers here and peaks. Each of those**
:45:52 **is an additional impurity that has been developed as a**
:45:59 **result of the photostability study. Specifically -- well,**
:46:04 **different impurities. Right?**
:46:05 A. **That is correct.**
:46:05 Q. **The sample that you were talking about in Column 2 was**

:46:13 not exposed to UV lighting?
:46:16 A. That's correct. That's also a different lot number
:46:19 than what was in the clear glass vials.
:46:24 Q. Am I correct that the IND here is not prior art as you
:46:32 understand it?
:46:35 A. That is correct.
:46:35 Q. You made no particular use this morning of the rate
:46:52 constant in the Maas article. Is that so?
:46:55 A. Not this morning.
:46:56 Q. You have in the past, in your deposition and pretrial
:47:01 discovery. Is that correct?
:47:03 A. That is true.
:47:03 Q. To that extent, you have modified your views and
:47:08 limited them to what you testified to today. Isn't that so?
:47:14 A. I don't believe I have modified my views at all.
:47:16 Q. Let me turn back, if I might -- we may come back to
:47:22 this, I would hope not -- but let me ask you some questions
:47:25 about your testimony yesterday.
:47:27 First of all, you focused on four particular
:47:30 batches of Ribomustin, didn't you? And you identified those
:47:34 numbers. You identified them from Table 13 in the '270
:47:41 patent, which is JTX-005, didn't you?
:47:45 A. That is one of the references that they were
:47:48 identified, yes.
:47:49 Q. Let's take a look at Table 13 in JTX-005. These are

:48:16 **the four lots that you were focused on and have been focused**
:48:21 **on for purposes of your opinion. Is that correct?**
:48:24 A. **That's correct.**
:48:24 Q. **These lots also appear in PTX-291, if we could take a**
:48:33 **look at that briefly, and specifically at Page 257, which is**
:48:42 **probably the Bates number in the lower right hand.**
:48:54 **Actually, while we are on this page -- you can**
:48:58 **take down the patent -- while we are on this page from**
:49:02 **PTX-291, if you look at the top, apropos of our discussion a**
:49:07 **few minutes ago, those six-digit numbers that we see, the**
:49:11 **first two are lot numbers from Ribosepharm and from**
:49:15 **Thymoorgan, not from -- the third one as well, not from**
:49:19 **Thissen. Correct?**
:49:20 A. **Yes.**
:49:21 Q. **And does that further satisfy you that those lots are**
:49:24 **likely not from Thissen?**
:49:26 A. **Yes.**
:49:26 Q. **And accordingly, not in the hands of Salmedix at any**
:49:30 **time, correct, based on the testimony? So far as you know?**
:49:37 A. **Based on the testimony, sure.**
:49:38 Q. **Now, the lots that you were focused on appear here, do**
:49:44 **they not? And if we go down about five lines, four lines,**
:49:48 **perhaps, we see Lot 02K27, that is one of the batches on**
:49:54 **which you rely, is it not?**
:49:55 A. **Yes, it is.**

:49:56 Q. **And then 03C08, 03H07?**

:50:17 **MR. WARE: Excuse me, Your Honor.**

:50:21 **THE COURT: Yes.**

:50:38 **BY MR. WARE:**

:50:40 Q. **I misdirected you. Could you look at Page 263. In any event, you see here in the left-hand column, among these are the four batches on which you relied. Correct?**

:51:01 A. **I do see them.**

:51:02 Q. **Each of these has, in the right-hand column, HP1 values. Isn't that so?**

:51:09 A. **Yes, it does.**

:51:11 Q. **And each of those exceeds the 0.9 percent as written. Is that correct?**

:51:19 A. **From Thissen and above, that is correct.**

:51:23 **So that just simply means that at the time that those values were taken, that was the HP1 value.**

:51:32 Q. **Very well. With respect to these four batches, you have no information as regards to where the sale of these took place, do you?**

:51:55 A. **I do not.**

:51:56 Q. **And so these sales may have occurred in Germany. Isn't that so?**

:52:05 A. **Are you talking about the sale of Ribomustin to the general public?**

:52:15 Q. **No. What I am talking about is these four batches**

:52:18 **which were used by Salmedix at some point for purposes of**
:52:21 **testing. Those came from Fujisawa, did they not, pursuant**
:52:26 **to the license agreement that you discussed?**
:52:29 A. **That would be my understanding.**
:52:30 Q. **Let's look at JTX-37, which is that license agreement,**
:52:35 **and specifically to Article 15 in the first instance.**
:52:49 **Have you had a chance to get there?**
:52:50 A. **No. Can you direct me to the tab?**
:52:52 Q. **Sure.**
:52:55 **THE COURT: It's Tab 37.**
:53:03 **BY MR. WARE:**
:53:04 Q. **6. In any event, this provision simply provides that**
:53:12 **German law will apply to the agreement. Isn't that so?**
:53:16 A. **That is my understanding.**
:53:18 Q. **And if we go back to Article 4 at Page 8 of the**
:53:35 **document, Bates Page 6559, to Subparagraph (9), I think you**
:53:47 **spoke about this yesterday as well. Correct?**
:53:50 A. **Yes, I have.**
:53:51 Q. **What 9(i) says is, Pursuant to this agreement bulk**
:53:57 **compound, meaning the active pharmaceutical ingredient, will**
:54:02 **be sold to or made available to Salmedix under the**
:54:06 **agreement. Correct?**
:54:08 A. **Correct.**
:54:08 Q. **And what the next paragraph, (ii), says, is that**
:54:15 **unlabeled vials of formulation of the compound will be made**

:54:20 **available. Isn't that so?**

:54:21 A. **That is true.**

:54:21 Q. **And the price term is cost plus 15 percent and it says FCA?**

:54:28 A. **Correct.**

:54:29 Q. **You have enough experience in commercial transactions like this to know that FCA means that the title to the goods transfers at the point of shipment. Isn't that so?**

:54:38 A. **That is my understanding.**

:54:41 Q. **And accordingly, if these shipments came from Fujisawa Deutschland, then pursuant to the license agreement, that transfer of title and ownership and risk occurred in Germany, did it not, as you understand it?**

:54:48 A. **Or wherever the warehouse would be.**

:54:56 Q. **Fine. But you have no reason to believe that this sale or that transfer of risk or title occurred in the United States. Correct?**

:54:59 A. **That is correct.**

:55:01 Q. **Under the licensing agreement -- well, all of the batches that were made available to Salmedix were subject to the license agreement so far as you know. Correct?**

:55:06 A. **That would be correct.**

:55:10 Q. **And you were present when Dr. Kabakoff testified that these were for development purposes. Isn't that so?**

:55:11 A. **I heard him say that.**

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:55:46 Q. **And yesterday you testified that there were about 7000**
:55:50 **vials made available. In the world of clinical trials,**
:55:54 **based on your experience, that is not a large number of**
:55:57 **vials, is it, because you have multiple patients, they are**
:56:01 **getting multiple doses, that is well within reason, is my**
:56:05 **point, of a clinical trial only. Isn't that correct?**
:56:09 A. **Yes.**
:56:09 Q. **In fact, multiples of that might be necessary for**
:56:13 **clinical trials, depending upon how many there are. Isn't**
:56:16 **that so?**
:56:17 A. **That would be true.**
:56:18 Q. **So the numbers themselves that you gave us, which you**
:56:22 **added up to 7000, that doesn't mean anything in terms of**
:56:26 **this being a commercial sale versus an experimental effort.**
:56:30 **Isn't that correct?**
:56:33 A. **I just look at it. It was a transfer. I understand**
:56:37 **the definition of commercial sale is something that will be**
:56:41 **defined by the Court.**
:56:43 Q. **So let's follow the transfer. In any event, to your**
:56:47 **understanding, all of these batches were transferred**
:56:50 **pursuant to the license agreement. You are not aware that a**
:56:52 **single vial ever was used for any purpose other than the**
:56:56 **experimental purposes defined here and defined in the**
:57:00 **clinical trials regarding which you have seen documents.**
:57:06 **Correct?**

:57:07 A. That would be correct.
:57:07 Q. You don't know of any vial ever that was sold on any
:57:10 basis by Salmedix. Right?
:57:14 A. That is true.
:57:15 Q. And you are well aware that the FDA had not approved
:57:19 Ribomustin for sale in the United States. Correct?
:57:24 A. Certainly not in 2004.
:57:27 Q. Are you saying it's now approved, Ribomustin?
:57:31 A. Oh, Ribomustin? No. Well, as Treanda.
:57:40 Q. Let me ask you to look, if you would, at JTX-33.
:57:59 A. Can you point me to a tab?
:58:04 THE COURT: It's Tab 33, JTX-33.
:58:11 THE WITNESS: Thank you.
:58:11 THE COURT: In the white binder.
:58:14 BY MR. WARE:
:58:15 Q. You have it in the cross binder, I think.
:58:18 A. Thank you.
:58:18 Q. And you recognize JTX-33, don't you?
:58:35 A. This appears to be a section -- I don't have the
:58:38 title. Is this the section of the IND or NDA?
:58:44 Q. The NDA, I believe.
:58:47 A. Thank you.
:58:47 Q. In any event, at Page 233, we again see the lots on
:58:53 which you have relied. Isn't that so? If you need some
:59:02 help here, about three lines down here, you see 02K27, which

:59:09 **is the lot about which you have talked the most, I think?**
:59:11 A. **Yes.**
:59:11 Q. **And then below the white line under Clinical Trials, you see the first three lots there, 03C08, 03H07 and 03H08. Those are the other three lots about which you have testified. Correct?**
:59:29 A. **Correct.**
:59:29 Q. **And you see on this document, it says, it describes these as a summary of bendamustine hydrochloride for injection batches "used in pivotal and supportive clinical trials."**
:59:45 **Correct?**
:59:45 A. **That's correct.**
:59:46 Q. **And you have no reason to believe that all of these were not used entirely in those investigational contexts. Correct?**
:59:53 A. **Well, I have seen documentation --**
:59:57 Q. **Hang on a second. If I am not correct, tell me I am not correct and we will go from there.**
:00:03 **Am I right that so far as you know, all four of these batches were used for investigational purposes in the clinical trials by Salmedix?**
:00:14 A. **That statement is correct.**
:00:29 Q. **Among the studies that was done, let me ask you to look at Plaintiff's Trial Exhibit 310, which I think is a**

:00:41 **dose response study. The Bates page is 795. It is at Tab**
:00:53 **310 in your binder.**
:00:54 A. **I have it.**
:00:55 Q. **This is an example, is it not, of some of the studies**
:01:09 **that were done on behalf of Salmedix during the course of**
:01:13 **this investigational stage? Correct?**
:01:19 A. **That is correct.**
:01:20 Q. **And this particular study has to do with the efficacy**
:01:24 **of bendamustine against tumor models in mice. Right?**
:01:38 A. **Yes, that is correct.**
:01:39 Q. **Studies of this nature and comparable studies are**
:01:42 **often used as precursors to human clinical trials. Is that**
:01:47 **so?**
:01:48 A. **That is true.**
:01:48 Q. **Let me ask you next to -- I want to talk to you about**
:01:55 **the '270 patent and your opinions there with respect to**
:01:58 **obviousness.**
:02:00 **As I understand part of your argument, it is**
:02:03 **that the '270 patent claims that you have identified are**
:02:07 **anticipated because these four batches that you have talked**
:02:12 **about are prior art because, in your view, they were**
:02:17 **commercially sold. Have I got that? If that's confusing, I**
:02:32 **can try again.**
:02:33 A. **Please try again.**
:02:35 Q. **All right. One of the reasons for which you relied on**

these four batches is you say these were commercially sold in the United States prior to the critical date, therefore, they are prior art, therefore, I can rely on them for purposes of anticipation or obviousness or whatever other opinions. Right?

A. You used the phrase commercially sold.

Q. Let's say transferred.

A. Transferred. They were transferred, they were disclosed in the patent. Confidential information from Salmedix describes that transfer.

Q. And the '270 patent, Claim 1, is talking about a composition after reconstitution, isn't it?

A. That is correct.

Q. I guess we should go back to the '270 patent to Column 30, to your Table 13. There you pick out a particular batch. And that's 02K27. And you point us to the HP1 level of 0.93. Is that correct?

A. That's correct.

Q. And then it's your opinion that 0.93 is right at the claim limitation of 0.9. Correct?

A. It is about 0.9.

Q. But when you say "about," you treat it as equivalent to 0.9, do you not?

A. I do.

Q. Do you know how this is dissolved for purposes of this

:04:17 **test, as spelled out in the patent?**

:04:19 A. **For this test, it's dissolved in methanol.**

:04:22 Q. **And you know that methanol could not be part of a pharmaceutical composition. Right? It would not be approved?**

:04:30 A. **Well, one would not inject methanol.**

:04:33 Q. **Right. So if you were making a pharmaceutical composition, while you might use it for a test, you wouldn't use it ultimately as part of the bulk solution or for that matter to reconstitute or dilute. Right?**

:04:50 A. **Not for administration to humans.**

:04:53 Q. **That's the whole idea here, isn't it? We are trying to make a medication?**

:04:57 A. **But we have to test that medication to see what the levels of potency and impurities are.**

:05:03 Q. **The solution tested in Table 13 is certainly not dissolved in water. Isn't that so?**

:05:11 A. **That is correct.**

:05:11 Q. **And, typically, for purposes of reconstituting Ribomustin or, for that matter, Treanda, it would be reconstituted in water for injection. Correct?**

:05:27 A. **That would be the first step of the reconstitution.**

:05:29 Q. **If you were to reconstitute even this batch in water, you would expect to get the HP1 impurity. Right?**

:05:41 A. **That is correct.**

:05:41 Q. **And regardless of Table 13, you would expect that**
:05:50 **impurity to continue to grow the longer that that product is**
:05:53 **exposed. Isn't that so?**
:05:56 A. **When you say exposed, it's exposed to water?**
:05:59 Q. **Yes, exposed to water.**
:06:01 A. **Yes.**
:06:01 Q. **Did you, in the course of your investigation, look at**
:06:08 **the purity -- do you know when that experiment was done,**
:06:12 **this particular experiment, that is the experiment that is**
:06:21 **displayed in Table 13?**
:06:22 A. **The specific date I do not recollect.**
:06:25 Q. **Do you have your -- you don't have your report up**
:06:28 **there, do you?**
:06:29 A. **I do not.**
:06:30 **MR. WARE: Your Honor, may I?**
:06:31 **THE COURT: Yes.**
:06:46 **BY MR. WARE:**
:06:48 Q. **If you would read to yourself the bottom paragraph,**
:06:51 **does that remind you that in the course of your**
:06:54 **investigation for purposes of this case, you did, in fact,**
:06:58 **determine when the analytical work was done?**
:07:02 A. **Yes. This is a paragraph, Paragraph 364, that is a**
:07:08 **review of --**
:07:10 Q. **That's okay. What I am asking you really is not the**
:07:13 **substance of that report. My question is, does it refresh**

your recollection as to the date on which the analytical work was done resulting in 0.93 as depicted in Table 13?
A. Yes. This says that the analysis was performed December 20th, 2004.
Q. And that's an investigation that you made at the time of laboratory notebooks, including Lucy Zhao's laboratory notebook. Correct?
A. Correct.
Q. Now, when you looked at this 0.93 number in Table 13, it is the lowest of the four samples, is it not?
A. It is.
Q. And did that suggest anything to you about whether that might be an outlier, given that all the other three samples are considerably higher?
A. No, I did not consider that as an outlier. I considered that a factual number.
Q. Let me ask you to look at -- well, did you look at any batch manufacturing records?
A. I believe I did.
Q. Did you look at the batch manufacturing record for this particular batch, if you know?
A. I do not recall.
Q. Let me direct you to PTX-818. I wonder if you could confirm for me whether or not this is the batch record for Lot 02K27 that we just saw in Table 13, which resulted in a

:09:12 **0.93 impurity level?**

:09:19 A. **Well, it's not a batch record.**

:09:24 Q. **It's a batch report, is it not, from the manufacturer?**

:09:28 A. **It looks to me like a certificate of analysis.**

:09:31 Q. **Very good. I think that's an appropriate correction. It's a certificate of analysis from the manufacturer investigating the purity, including the level of HP1, at the time of manufacture or post-manufacturing. Correct?**

:10:14 A. **So this document is dated on the next page in 2002.**

:10:20 Q. **Well, you tell me. It's not dated 2002. It says that the manufacturing date was November 2002, doesn't it?**

:10:29 A. **Oh, I was referring to the signature, the date of the signature of the quality assurance.**

:10:37 Q. **In any event, there is no magic to this, it is a certificate of analysis, it relates to Lot No. 02K27, and it identifies the HP1 impurity level at that time. Correct?**

:10:49 A. **That it does.**

:10:50 Q. **And this is, according to you, the lot that was examined by Salmedix in the laboratory on December 20th, 2004. Correct?**

:11:00 A. **Correct.**

:11:01 Q. **And at that time, this lot was expired, was it not? The lot on which the 0.93 was calculated?**

:11:22 A. **That would be correct. It was one month past its expiring date or its shelf life.**

:11:27

:11:29 Q. **So that reading or evaluation of 0.93 is a result of**
:11:35 **an analysis of a batch that had already passed its**
:11:38 **expiration date. Correct?**
:11:40 A. **That is correct.**
:11:40 Q. **But you did not choose to use the 1.6 in the batch**
:11:48 **record itself -- excuse me, in the certificate of analysis**
:11:51 **itself for the HP1 level in your analysis?**
:12:03 A. **That is true. But I do not know the reconstitution**
:12:10 **method of how this 1.6 was calculated.**
:12:14 Q. **Okay. But you were trying to make a point with us**
:12:19 **today, and yesterday, and you looked at Lot 02K27, and you**
:12:26 **picked out the 0.93 because it's close to .9. Correct?**
:12:31 A. **Correct.**
:12:31 Q. **But you did not refer nor consider the certificate of**
:12:36 **analysis that showed that was an expired batch. Correct?**
:12:41 A. **That is correct.**
:12:42 Q. **Let me ask you, if you would, please, to go to the**
:13:05 **Maas paper, which I believe is Exhibit 146. I just want to**
:13:17 **be sure a couple of things are clear from the article.**
:13:34 **Do you have that before you?**
:13:35 A. **I do.**
:13:35 Q. **Let me direct you, if I might, first of all, to Page**
:13:40 **005. Do you have that before you?**
:13:43 A. **I have it.**
:13:43 Q. **And there we see a diffractogram. You explained**

yesterday that that -- excuse me, a chromatogram. And you explained yesterday that the first peak on the far left of that is the HP1 impurity. Right?

A. Correct.

Q. And the next one is some kind of an impurity.

Can we highlight the three little peaks, or enlarge it? Thank you.

The one that's above 0.4 is HP1. Correct?

A. Correct.

Q. As you understand her paper?

A. Yes.

Q. The large one is Ribomustin?

A. Bendamustine.

Q. Excuse me. Bendamustine. And the middle one is some kind of impurity as a result of the synthesis of the product, according to the Maas paper. Right?

A. That is correct.

Q. Now, this analysis -- she then develops a rate constant, a calculation of how quickly HP1 will form. Is that right?

A. Well, no, it's not. She calculates a rate constant for how rapidly bendamustine will disappear, which is inversely proportional to the amount of HP1 formation.

Q. In any event, the solution she uses is a fully diluted solution in saline, it is not in pure water. Correct?

A. That is correct. It is as per the product monograph.
Q. And on the following page, on Page 006 in the middle, under Discussion, about a third of the way down that paragraph, there is a sentence which begins "All the tested solutions show the pH value of 4," and then the next sentence, "In preliminary tests, the hydrolysis of bendamustine was monitored," "in water for injection purposes was monitored."
And she goes on to say basically in the next couple of lines that that impurity will develop significantly quicker in water than it does in saline. Correct?
A. That's correct.
Q. And you certainly don't dispute that, do you?
A. No, I do not.
MR. WARE: Your Honor, may I have just a moment? I may be pretty well done here.
THE COURT: Okay.
BY MR. WARE:
Q. I think you did say yesterday that in the Maas paper, she does not calculate any absolute value of the impurity HP1 or any other value. Isn't that so?
A. That is correct.
Q. And that's because -- well, it's because she sets time zero, meaning the first point at which she begins to

:16:55 **evaluate at a hundred percent. Right?**

:17:00 A. **Well, she normalizes bendamustine to a hundred**

:17:03 **percent.**

:17:03 Q. **What that means in a nutshell is that rather than her**

:17:07 **trying to figure out how much impurity may have already**

:17:11 **gotten into the solution, she simply starts her testing as**

:17:16 **if that was a hundred percent pure and measures from there.**

:17:20 **Correct?**

:17:22 A. **Yes. Maas doesn't care, if you will, how much was**

:17:27 **present beforehand. You are absolutely correct. She starts**

:17:32 **at a hundred percent bendamustine.**

:17:34 Q. **You would agree that the documentation, so far as you**

:17:40 **know, to which Mr. Brittain had access and to which Salmedix**

:17:43 **had access was confidential, were confidential documents.**

:17:48 **Right?**

:17:49 A. **That is correct if we discount the prior art like the**

:17:54 **Maas article and the Gust.**

:17:56 Q. **Right. But to be more clear, the documents received**

:18:00 **from Fujisawa pursuant to the license agreement, so far as**

:18:04 **you know, were all confidential documents?**

:18:07 A. **That is correct.**

:18:07 Q. **And that includes the common technique document, the**

:18:11 **analogue to the NDA that we looked at. Isn't that correct?**

:18:17 A. **That is correct.**

:18:17 Q. **None of that information, to your knowledge, was made**

:18:24 **public at any time prior to the priority date or the**
:18:28 **critical date, as you described it. Correct?**
:18:31 A. **Correct.**
:18:34 Q. **You don't disagree that Mr. Brittain was required to**
:18:40 **do a number of experiments to develop his formulation. You**
:18:47 **have your reasons why that was present in the documents or**
:18:49 **could have been inferred from the documents, but you don't**
:18:52 **disagree that he had to do experimentation. Right?**
:18:57 A. **Once Salmedix made the decision.**
:19:00 Q. **Let me see if you can --**
:19:03 A. **I will answer your question directly. And that's:**
:19:09 **No. The reason --**
:19:11 Q. **Let me understand the "no." The no is you don't think**
:19:14 **he had to do any experimentation?**
:19:18 A. **Under one scenario.**
:19:20 Q. **Well, my question to you is different. Mr. Brittain**
:19:24 **had a series of documents and information from Fujisawa. He**
:19:29 **ended up with a formulation which becomes commercially**
:19:32 **Treanda. You don't contend that he didn't have to do any**
:19:37 **experimentation to get there. Isn't that right?**
:19:40 A. **I will agree to that.**
:19:42 Q. **And you don't contend that the Fujisawa documents in**
:19:48 **and of themselves showed the formulation which ultimately**
:19:52 **became Treanda?**
:19:54 A. **Not exactly.**

:19:55 Q. **Not exactly correct or you agree that they did not**
:19:59 **show it exactly?**
:20:00 A. **I agree that they did not show it exactly.**
:20:03 Q. **Your position is he could have inferred something from**
:20:07 **the documents, not that the particular formulation was**
:20:10 **itself present in the documentation. Correct?**
:20:13 A. **Correct.**
:20:16 Q. **You don't contend that the ultimate formulation**
:20:21 **developed by Mr. Brittain was not an improvement over**
:20:25 **Ribomustin, do you?**
:20:34 A. **I heard the "not an improvement." What Mr. Brittain**
:20:37 **did was an improvement. So maybe I am misunderstanding your**
:20:41 **question.**
:20:41 Q. **I think it is probably the fault of the questioner.**
:20:44 **We are in agreement that the work that Mr.**
:20:47 **Brittain did resulted in a formulation which was, in fact,**
:20:50 **an improvement over the preexisting Ribomustin?**
:20:53 A. **Yes.**
:21:10 **MR. WARE: May I have just a moment, Your Honor?**
:21:12 **THE COURT: Yes.**
:21:17 **(Pause.)**
:21:19 **MR. WARE: Thank you, Dr. Jarosz. That is all**
:21:23 **for now, at least.**
:21:24 **THE COURT: Mr. Sung, redirect.**
:21:28 **REDIRECT EXAMINATION**

BY MR. SUNG:

Q. **Dr. Jarosz, just a few questions based on Mr. Ware's questioning.**

You heard Mr. Ware refer you to the Lot 380800, and do you recall him asking you questions as to how it was reconstituted?

A. **Oddly enough, I lost recall of his questions on how it was reconstituted.**

Q. **Does it refresh your recollection if I say the question was directed to whether you knew it was reconstituted in methanol, acetonitrile, any particular solvent?**

A. **And I do not know how it was reconstituted.**

Q. **Pull up DDX-31 again, Mr. Vaughn.**

You testified earlier, Dr. Jarosz, that the data with respect to HP1 levels in this Lot 380800 were .48 percent. Is that correct?

A. **That's correct.**

Q. **And you testified earlier that the HP1 observed would represent that number in this demonstrative?**

A. **That is correct.**

Q. **Does it matter to you whether -- if I can rephrase that, does it matter to you what solvent Lot 380800 is dissolved in?**

A. **Not when it's a test method to determine the HP1**

observed.
Q. And why is that?
A. Because that is taking a snapshot in time to determine the exact amount of, if the intention is HP1, to determine that level. And that is the maximal level that exists in that sample.
Q. So at any earlier time point, it would be either the same or less?
A. That is correct.
Q. If we can turn to the '270 patent. That is Tab 2. If we can go back to Table 13. Dr. Jarosz, while Mr. Vaughn is pulling up that table, do you recollect in your conversation with Mr. Ware that he was referring you to the Batch 02K27?
A. Yes.
Q. And that you had testified that the 02K27 data that is represented here, .93, is from an expired lot?
A. That is correct.
Q. Are you able to reach a conclusion whether or not the applicants for the '027 patent submitted data to the U.S. Patent and Trademark Office on an expired lot?
MR. WARE: Objection.
THE COURT: Basis.
MR. WARE: I can't imagine how he would know.
THE COURT: That's overruled, Mr. Ware.
THE WITNESS: So, yes. There has been earlier

:25:14 testimony, the certificate of analysis for release was dated
:25:17 in November of 2002. And this is December 2004. Ribomustin
:25:28 has a two-year expiring date. So it's one month past the
:25:34 expiring date. But I think I need to explain that the
:25:38 expiring date doesn't necessarily mean that the product is
:25:42 not still usable for its intended purpose. One could get an
:25:48 extension on that expiring date, given data.
:25:53 So what this .93 represents to me, even though
:25:58 it was taken one month post expiring date, it's still a real
:26:06 value.
:26:06 Q. Aside from it being a real value, Dr. Jarosz, is this
:26:11 still actual data from an expired lot?
:26:15 A. Yes, it is.
:26:17 Q. Dr. Jarosz, do you recall in your discussion with Mr.
:26:18 Ware that the Treanda formulation represented improvement
:26:24 over the Ribomustin formulation?
:26:28 A. Yes.
:26:28 Q. To the extent that Claims 1, 3 and 5 of the '270
:26:35 patent also cover Ribomustin, were you able to reach a
:26:43 conclusion whether or not at the time of a sale Ribomustin
:26:49 was ready for patenting?
:26:51 A. Yes, it was ready for patenting.
:27:11 MR. SUNG: No further questions, Your Honor.
:27:13 THE COURT: Thank you, Mr. Sung.
:27:14 Doctor, thank you. You are excused. Please be

:27:17 **careful stepping down.**

:27:18 **THE WITNESS: Thank you.**

:27:18 **(Witness excused.)**

:27:20 **MR. SUNG: Your Honor, if I may turn the podium over to Mr. Cwik.**

:27:23

:27:24 **MR. CWIK: Your Honor, Joe Cwik on behalf of InnoPharma. Your Honor, that ends the defendants' case in chief at this point in time.**

:27:26

:27:29

:27:30 **So at this point, Your Honor, the rules give us the opportunity to move for judgment based on the evidence that has been presented so far under Rule 52. If Your Honor is in a position at this point in time to make a ruling on a Rule 52 motion, we would like to move for judgment.**

:27:32

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:27:47 **THE COURT: Whether I am in a position or not, you can make a motion.**

:27:50

:27:51 **MR. CWIK: Specifically, Your Honor, the defendants would like to move for judgment on the obviousness of the asserted claims, specifically, the '190 patent Claims 5 and 8, the '863 patent Claim 1, the '270 patent Claims 1 through 5, 19 through 21, the '756 patent Claims 1 and 4.**

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:28:14 **In addition, the defendants move for judgment on anticipation by the Maas reference, that's on patent Claims 1, 3 and 5. The defendants also move for invalidity on the on-sale bar of the '270 patent, and that's on Claims 1, 7,**

:28:18

:28:23

:28:27

:28:33 **19. And the defendants also move for judgment based on the**
:28:36 **derivation theory on the '270 patent Claims 7, 19 through**
:28:42 **21, that the information was derived by Fujisawa.**
:28:46 **The basis for the defendants' --**
:28:50 **THE COURT: I will give you a chance, on that**
:28:52 **laundry list, to tell me which ones you really believe in**
:28:55 **and make a brief argument. Then I will hear from the other**
:28:58 **side. I can't imagine how you can seriously contend that**
:29:03 **you are entitled to JMOL on the on-sale bar at this point,**
:29:07 **given what we have just heard, for instance, to give you**
:29:09 **some guidance.**
:29:10 **MR. CWIK: Yes, Your Honor. I understand.**
:29:13 **Your Honor, I think the strongest evidence that**
:29:15 **we have presented so far has been on the obviousness of the**
:29:18 **asserted claims of the four formulation patents. We have**
:29:21 **seen evidence of the prior art Ribomustin product. It was**
:29:26 **very well known in prior art documents that we have shown**
:29:30 **that the Ribomustin product was having problems with**
:29:33 **reconstitution time and the Ribomustin product was known to**
:29:36 **be having issues with stability.**
:29:39 **Based on those problems, there was a strong**
:29:41 **motivation to improve the Ribomustin product. We have seen**
:29:45 **prior art references strongly suggesting and even stating**
:29:50 **that TBA could be known to solve stability problems in a**
:29:56 **water highly reactive molecule like bendamustine, and also**

that the prior art also stated that the reconstitution time could be improved by using TBA.

As far as reaching each of the specific claim elements of the claims, routine optimization, as has been presented by Dr. Kwan and Dr. Kamat, shows that routine optimization could have reached and gotten the --

THE COURT: Let me interrupt for a second. Doesn't part of your argument rest on your believe or assumption that I find all your witnesses credible?

MR. CWIK: That's correct, Your Honor.

THE COURT: And perhaps don't credit the other side?

MR. CWIK: Your Honor, I think the documents speak for themselves.

THE COURT: The documents without the accompanying testimony?

MR. CWIK: Your Honor, the documents and the Ribomustin product itself could lead to a finding of obviousness.

THE COURT: I disagree. Go ahead. Just that alone, I disagree strongly. Go ahead. I think the evaluation of the witnesses by the fact-finder is critical to resolving this case. Therefore, I cannot imagine how I am going to be able to render a JMOL ruling for either side, quite frankly, on virtually anything. There may be

:31:15 something you can call my attention to that makes sense to
:31:20 do to try to pare down the issues for me later on. If you
:31:23 can tell me one of those, I would be more than willing to
:31:28 grant you a ruling on obviousness. But not anticipation.
:31:33 MR. CWIK: I understand that, Your Honor.
:31:37 THE COURT: You have to make your record. I am
:31:41 being critical of the substance of your argument, not the
:31:43 fact that you are making it.
:31:45 MR. CWIK: Thank you.
:31:46 THE COURT: What do you want to say, Mr. Wiesen?
:31:48 MR. WIESEN: Your Honor, I will be very, very
:31:50 brief.
:31:52 I actually was a little confused to see the
:31:55 defendants stand up because they have the burden and I think
:31:57 we are getting ready to present our witnesses.
:31:59 THE COURT: I think you do. I don't think it
:32:01 was untimely. Go ahead.
:32:03 MR. WIESEN: We had not intended to move under
:32:05 Rule 52. We figured at this point we would let the case
:32:10 play out for the last day or two and hear all the evidence.
:32:12 If you are interested in hearing argument on any issue, we
:32:17 would be happy to present it. Our expectation was you would
:32:22 take it under advisement.
:32:23 THE COURT: Just a head's up. There may be a
:32:25 question or two that interests me. As you might imagine, my

:32:30 **fine law clerk and I have engaged in some dialogue. She**
:32:34 **happens to be a scientist, a very fine scientist. She**
:32:40 **attended some universities some of you may have attended.**
:32:44 **MR. WIESEN: I am happy to address any questions**
:32:46 **now.**
:32:46 **THE COURT: Not now. Not right at the moment.**
:32:49 **MR. WIESEN: That is all the response we have.**
:32:52 **THE COURT: Anything else?**
:32:54 **MR. WIESEN: Your Honor, I think the case now**
:32:56 **comes back to us.**
:32:57 **THE COURT: I think it does.**
:33:01 **Should we take a break?**
:33:02 **Let's do that.**
:33:04 **(Recess taken.)**
:55:03 **THE COURT: All right. Take your seats.**
:55:05 **Mr. Wiesen?**
:55:06 **MR. WIESEN: Your Honor, the plaintiffs call Dr.**
:55:08 **Tom Welton.**
:55:09 **THE COURT: Okay.**
:55:12 **MR. WIESEN: And while Dr. Welton takes the**
:55:14 **stand, if I could give a brief overview of the subject**
:55:16 **matter of his testimony.**
:55:18 **THE COURT: Good.**
:55:19 **MR. WIESEN: Dr. Welton will be our first**
:55:21 **witness responding to some of the arguments raised by**

defendants concerning the obviousness of the '190, '863 and '270 patent.

Dr. Welton will claim he's an expert in what are called solvent effects, and he'll specifically address only the effect of TBA or a person of ordinary skill in the art would know or learn about the effect of TBA on the degradation of bendamustine hydrochloride in the pre-lyophilization solution.

THE COURT: Okay.

MR. WIESEN: We've divided the issues among experts so there won't be overlap.

There are other issues Dr. Winter will address on Monday related to the issue of obviousness. Dr. Welton is testifying about just this one carved out issue to avoid any risk of overlap.

THE COURT: Okay.

THOMAS WELTON, having been duly affirmed as a witness, was examined and testified as follows ...

THE COURT: Good morning.

THE WITNESS: Good morning.

MR. WIESEN: Your Honor, I believe we've already distributed binders.

THE COURT: I think we're ready to go.

DIRECT EXAMINATION

:56:39 **BY MR. WIESEN:**

:56:43 Q. **Good morning, Dr. Welton. Could you state your name for the record, please?**

:56:45

:56:46 A. **Good morning. Thomas Welton.**

:56:48 Q. **Where do you live, sir?**

:56:49 A. **I live in London.**

:56:50 Q. **Are you currently employed?**

:56:51 A. **I am. I'm the Dean of the Faculty of Natural Sciences at Imperial College and a Professor of Sustainable Chemistry.**

:56:56

:56:59

:57:00 Q. **Is the Professor of Sustainable Chemistry a chaired professorship?**

:57:03

:57:05 A. **Yes.**

:57:05 Q. **What are your general responsibilities at Imperial College, London?**

:57:08

:57:08 A. **So I have my managerial responsibilities as an executive dean, but also I'm a teacher and researcher in the chemistry department.**

:57:12

:57:17

:57:18 Q. **And I wanted to step back for a few minutes and talk about some of your background. Your CV is located at PTX-252 in your binder if you need it.**

:57:23

:57:28

:57:36 A. **Sorry. Can you repeat that?**

:57:37 Q. **PTX-252.**

:57:39 A. **Yes.**

:57:44 Q. **Dr. Welton, what undergraduate degree do you hold?**

:57:47 A. **I have an honors Bachelor's degree from University of**
:57:52 **Sussex in chemistry.**
:57:53 Q. **Do you have any post-graduate degrees?**
:57:54 A. **I have a D.Phil. from the University of Sussex in**
:57:58 **chemistry.**
:57:58 Q. **Is the D.Phil. the same thing as a Ph.D. here in is**
:58:02 **the U.S.?**
:58:02 A. **It's precisely the same.**
:58:04 Q. **What was the scientific focus of your D.Phil.?**
:58:07 A. **I worked on the chemistry and spectroscopy of ionic**
:58:12 **liquids.**
:58:12 Q. **And just very briefly, what are ionic liquids?**
:58:15 A. **Ionic liquids are a recent type of solvent which are**
:58:19 **composed entirely of ions.**
:58:20 Q. **Did you do any post-doctoral research?**
:58:24 A. **I did.**
:58:24 Q. **Where?**
:58:25 A. **So I continued on at the University of Sussex as a**
:58:30 **postdoctoral research fellow, and then following that I**
:58:33 **moved to the University of Exeter as a demonstrator in**
:58:37 **organic chemistry.**
:58:38 Q. **What were your responsibilities at the university of**
:58:40 **Exeter?**
:58:41 A. **So primarily to teach students in the laboratory about**
:58:45 **laboratory techniques, distillations, those kinds of things,**

and to teach them in small group sessions that we call tutorials.

Q. And how long were you at the university of Exeter?

A. Two years.

Q. Where did you go next?

A. I went from there to Imperial College as the Lloyds of London Tercentenary Research Fellow.

Q. And what is a Lloyds of London Tercentenary Research Fellow?

A. So Lloyds of London, the well-known insurance organization, they have a charity arm called the Lloyds of London Tercentenary Research Foundation, and at that time this foundation was awarding fellowships to young academics to help them get their career kick-started.

Q. And how many fellowships were awarded in the year you received one?

A. Three.

Q. How many chemists received them?

A. One. Me.

Q. So I think that fellowship is wgeb you started at Imperial College London?

A. Absolutely.

Q. Can you describe the promotions you received during your time at Imperial College?

A. So at the end of the fellowship, I was appointed to a

:59:56 **lectureship at Imperial College in chemistry and then a**
:00:00 **senior lectureship and readership. A readership is roughly**
:00:03 **equivalent to your associate professor, and then on to the**
:00:08 **full chair.**
:00:09 Q. **And have you held any administrative positions at**
:00:12 **Imperial College?**
:00:13 A. **I have, indeed. I was the director of undergraduate**
:00:16 **studies for the chemistry department, which meant that I had**
:00:20 **responsibility for the oversight of the whole of the --**
:00:21 **well, all of the undergraduate degree program, because**
:00:25 **there's more than one in the department.**
:00:26 **Then I became the head of the department, and**
:00:28 **then following that, at the beginning of this year, I became**
:00:32 **dean of faculty.**
:00:34 Q. **And how big is that faculty that you are the dean of?**
:00:37 **How big is that group?**
:00:38 A. **So we have 1,300 staff, roughly 750 Ph.D. students, a**
:00:45 **similar number of master students, and about 3,000**
:00:49 **undergraduates, just under 3,000 undergraduates.**
:00:52 Q. **And do you still find time to teach and do research**
:00:59 **while you're the dean?**
:01:00 A. **Oh, absolutely. They're very important to me.**
:01:02 Q. **Have you focused your research efforts in any**
:01:04 **particular field?**
:01:06 A. **So my research is in the area of solvents and solvent**

:01:12 **effects, particularly, although not exclusively, with ionic**
:01:14 **liquids.**
:01:15 Q. **And you teach as well?**
:01:17 A. **I do, yes.**
:01:19 Q. **What subject?**
:01:19 A. **So I teach solvent effects.**
:01:22 Q. **To undergraduates?**
:01:23 A. **To undergraduates, first year undergraduates.**
:01:26 Q. **Have you authored any articles in your career?**
:01:28 A. **Yes, I have.**
:01:29 Q. **Approximately how many?**
:01:29 A. **About 110 at the moment.**
:01:32 Q. **And any books?**
:01:33 A. **Yes. So I'm the co-editor of a book called "Ionic**
:01:38 **Liquids in Synthesis," and I'm a co-author of a book called**
:01:43 **"Solvent and Solvents Effects in Organic Chemistry."**
:01:47 Q. **Have you received any awards or honors during your**
:01:49 **academic career?**
:01:50 A. **I have. I was American Chemical Society New Voice in**
:01:56 **Chemistry, which is a particular honor being a foreigner.**
:02:00 **I'm a fellow of the Royal Society of Chemistry.**
:02:03 **I won the RSC Sir Christopher Ingold**
:02:08 **Lectureship, which is th0e lectureship for Inorganic**
:02:11 **chemistry.**
:02:12 **I have an award from the German Sciences,**

DFG. A more recent award from the RSC for Chemistry. And this year I've just been made one of the 175 Faces of Chemistry for the RSC.

Q. Could you briefly describe what got you the award as one of the 175 Faces of Chemistry for the RSC?

A. So partly for academic standing, but really through my work on diversity in science.

Q. Are there any other boards or organizations you work with in your professional career?

A. So I'm a member of the Council of Royalty Society of Chemistry, which means I'm a trustee of the charity.

I'm a trustee of the charity for Lloyds of London Tercentenary Research foundation. You have to pay back from where you got. And I'm the current chair of an organization called the heads of Chemistry U.K.

Q. What is the heads of Chemistry U.K.?

A. So it's an organization that brings together all of the heads of all of the chemistry departments throughout the U.K. We meet about three times a year to discuss issues around chemical education, chemical research, government policy, those kind of things.

Q. How many universities participate in that organization?

A. There's about 60.

Q. We talked for a minute about publications you have.

:03:30 **Do any of those publications generally relate to the issues**
:03:33 **you're going to talk about today?**
:03:34 A. **Yes. I have a number of publications on -- well, most**
:03:38 **of my publications are on solvents and solvent effects, some**
:03:42 **on reactions in ionic liquids, substitution reactions.**
:03:46 Q. **And we'll get to the explanation of nucleophilic**
:03:49 **substitution reactions in a couple minutes, which I think**
:03:52 **came up previously.**
:03:53 **Have you done any consulting work with the**
:03:55 **pharmaceutical industry?**
:03:56 A. **Yes, I have.**
:03:57 Q. **And without violating any confidentiality, could you**
:04:00 **describe just generally the type of work?**
:04:02 A. **So mostly on solvent replacement in chemical**
:04:11 **synthesis, but I have literally just in the last month been**
:04:16 **working with GSK on -- some work on novel solvent effect**
:04:23 **formulations.**
:04:24 Q. **And I think we looked already at PTX-252. Can you**
:04:31 **just confirm that's an accurate copy of your CV?**
:04:34 A. **It requires a couple of extra papers that have come**
:04:40 **out recently. Of course, the citations can change on a**
:04:44 **daily basis, but it as description of my career.**
:04:48 **MR. WIESEN: And, your Honor, with just that**
:04:49 **background, we'd tender Dr. Welton as an expert in the field**
:04:52 **of chemistry and solvent effects in particular.**

:04:56 **MR. DAIGNAULT: No objection, your Honor. I am**
:04:58 **just going to wait.**
:05:01 **THE COURT: All right. The doctor is accepted**
:05:03 **as an expert in those fields.**
:05:04 **THE WITNESS: Thank you.**
:05:05 **BY MR. WIESEN:**
:05:06 Q. **Dr. Welton, have you been engaged as an expert in this**
:05:08 **case?**
:05:08 A. **Yes, I have.**
:05:09 Q. **And if you look in your binder at JTX 1, 5 and 6, do**
:05:17 **you recognize these patents?**
:05:20 A. **Yes, I do.**
:05:20 Q. **They're the '190, '270, and '863 patents,**
:05:24 **respectively?**
:05:25 A. **They are. They are, indeed.**
:05:27 Q. **Have you worked with counsel to prepare some slides to**
:05:29 **help with your testimony today?**
:05:30 A. **Yes, I have.**
:05:31 Q. **All right. And what question have you been asked to**
:05:40 **consider?**
:05:41 A. **So I've been asked to consider whether a person of**
:05:44 **ordinary skill in the art would consider these claims to be**
:05:48 **obvious.**
:05:49 Q. **And what conclusion did you reach?**
:05:52 A. **No, they're not.**

:05:53 Q. **And, Dr. Welton, as I explained to the Court before, I**
:06:00 **know you provided opinions on a number of issues in your**
:06:02 **reports, but for purposes of trial, we're going to limit you**
:06:04 **to just the issue as I described it, the effect of TBA in**
:06:08 **the pre-lyophilization solution and what a person of**
:06:11 **ordinary skill in the art would know about it.**
:06:14 A. **Okay.**
:06:15 Q. **With that in mind, can you summarize for the Court the**
:06:22 **basis for your conclusion.**
:06:24 A. **So I don't believe that the claims are obvious because**
:06:29 **the information in the literature doesn't give you a**
:06:34 **sufficient predictive capacity or likelihood of success of**
:06:38 **using TBA, and it also, there are potential other**
:06:44 **alternatives available in the literature that one might also**
:06:47 **explore.**
:06:47 Q. **In your opinion, sir, based on the references you**
:06:52 **reviewed, would it have been obvious to use tertiary butyl**
:06:56 **alcohol as a co-solvent in the pre-lyophilization solution**
:07:00 **for bendamustine hydrochloride?**
:07:02 A. **Absolutely not.**
:07:02 Q. **Before we get into the substance of the opinion, I**
:07:05 **just want to make sure we do a little background,**
:07:08 **perspective from what you are offering your opinion.**
:07:10 **Did you consider the definition of a person of**
:07:12 **ordinary skill in the art in this case?**

:07:14 A. **Yes, I did.**
:07:14 Q. **And if we could have slide PDX-9-4. What definition**
:07:21 **of a person of ordinary skill in the art did you apply?**
:07:23 A. **This one. A person with a Bachelor's degree. Do you**
:07:25 **want me to read it?**
:07:26 Q. **If you could, but let me ask you to read it slowly for**
:07:29 **the court reporter?**
:07:29 A. **All right. "A person with a Bachelor's degree in**
:07:32 **pharmaceutical sciences or a related field and at least five**
:07:35 **years' experience formulating, characterizing or analyzing**
:07:38 **pharmaceutical products, or a Master's degree or a Ph.D. in**
:07:42 **pharmaceutical sciences or a related field and at least**
:07:46 **three years' experience formulating, characterize goes or**
:07:49 **analyzing pharmaceutical products. This person of ordinary**
:07:56 **skill in the art would have access to and/or collaborate, as**
:07:58 **needed with individuals in other areas of science, including**
:08:01 **medicine and drug development."**
:08:02 Q. **Now, Dr. Welton, have you spent your career as a**
:08:06 **pharmaceutical formulator?**
:08:07 A. **No, I have not.**
:08:09 Q. **In your opinion, sir, despite that, do you still**
:08:12 **generally meet this definition of a person of ordinary skill**
:08:14 **in the art?**
:08:14 A. **Yes, I do.**
:08:15 Q. **Why do you say that?**

A. **So I make a lot of chemical products. I do synthesis, and as such you have to analyze those products.**

Some of those products have been pharmaceutical products, and I have supervised students who have done the same, including Ph.D. students, undergraduate students who have, either at in college or during the time that they're in laboratories in a pharmaceutical company. I believe I meet the definition sufficiently.

Q. **Whether you meet the definition or not, are you comfortable offering opinions about what a person of ordinary skill in the art would know and understand?**

A. **Oh, yes, yes.**

Q. **Why?**

A. **Well, throughout my career, I've known a number of formulators in the pharmaceutical industry. I teach people who go on to become pharmaceutical formulators. And I have even had discussions with hospital pharmacists, pharmacy students, pharmacy students about the use of a highly unstable oncology drug and how its fundamental chemistry interacts with the patient.**

Q. **And you're aware that the defendants have offered some slightly different definitions of a person of ordinary skill in the art?**

MR. WIESEN: If we could have PDX-9-5, please.

THE WITNESS: Yes, I am aware of it.

:09:49 **BY MR. WIESEN:**

:09:49 Q. **And would it impact your opinion if the Court adopts one of these definitions versus the definition you've offered?**

:09:55 A. **No. That is fine.**

:09:57 Q. **And similarly, are your skills and experience consistent with the defendants' definitions as well?**

:10:03 A. **I believe so. Yes. They point out organic chemistry, which I've done, medicinal chemistry, related fields. The one -- experience, one combines that with experience, yes, I believe so.**

:09:55 Q. **Dr. Welton, did you also focus your analysis on a particular time period for what a person of ordinary skill in the art would know?**

:10:05 A. **I did. So the period prior to the publication of these patents, so I am taking that to be the beginning of 2005.**

:10:12 Q. **Thank you, Dr. Welton.**

:10:18 **Were you present in the courtroom when Dr. Kamat and Dr. Kwan testified about how a person of ordinary skill in the art would choose a solvent to make the pre-lyophilization solution of bendamustine hydrochloride?**

:10:30 A. **Yes, I was.**

:10:31 Q. **Did you agree with their testimony that the person of ordinary skill in the art would choose a TBA-water**

co-solvent system?

A. No, I don't agree with them.

Q. Why not?

A. Because, as I said before, there is insufficient information in the literature to allow one to have a predictive capacity of success, but there is also information which tells you that there are other alternatives that you might try.

Q. So let's back up and talk for a couple minutes just about the concept of solvent effects.

If we could have PDX-9-7.

Could you describe for the Court again fairly generally what the study of solvent effects is all about?

A. The study of solvent effects is, as counsel might expect, how solvents can affect the chemistry that is observed within them, particularly, we focus on things in synthesis like the rate of the reaction, the yield of the reaction, the selectivity of different products.

In a practical sense, it's normally talked about in the sense of what happens when I change from solvent A to solvent B and what differences might I expect to see.

Q. Just to define a couple of terms, what is a solvent?

A. A solvent is a material in which you are dissolving something, and a solute is the material that is being dissolved.

:12:00 Q. **And in your opinion, sir, are solvent effects**
:12:03 **something that a formulator would consider during drug**
:12:07 **development?**
:12:07 A. **Oh, absolutely, yes.**
:12:08 Q. **Why?**
:12:10 A. **Because when you are having -- when you have any kind**
:12:13 **of solution -- so a solution is the homogeneous phase made**
:12:18 **by the solvent and solute. When you have any kind of**
:12:21 **solution, then you have to take into account the solvent's**
:12:25 **effects on that solution.**
:12:26 Q. **In your opinion, sir, would a pharmaceutical**
:12:28 **formulator be aware of and know about solvent effects?**
:12:31 A. **Oh, yes, of course, they would.**
:12:33 Q. **How do you know that?**
:12:34 A. **Well, they come from degree programs that you would**
:12:38 **teach that kind of stuff in them.**
:12:40 Q. **In fact, do you teach that kind of stuff?**
:12:43 A. **I teach it, as I say, to my first-years, as well as to**
:12:47 **my advanced classes.**
:12:50 Q. **Can you just generally describe how solvents create a**
:12:54 **chemical environment that needs to be considered?**
:12:56 A. **If you think about any solution, I always use the**
:12:59 **example of my cup of tea when I am talking to the students,**
:13:02 **the vast majority of the material in the solution is the**
:13:07 **solvent. And the solutes are present in a relatively minor**

amount, often in a microscopically minor amount.

So the way -- the experience that the solute molecules have is of a surroundings of solvent, not surroundings of more of the same solute. They are dispersed.

So that environment is dominated by the solvent. And so the solvent itself can be -- well, determining sometimes in what happens, but strongly influential always.

Q. What step of the lyophilization process have you looked at to consider solvent effects in this case?

A. So I have considered the pre-lyophilization solution. So if you like, the thing that happens until the point at which you bring it to the machine.

Q. Why is it important to focus on that pre-lyophilization solution?

A. So the solution would be existing for quite some time between the time it starts to dissolve and when it finally begins the lyophilization. So there is plenty of time for the reactivity of the solution to start impacting upon what's in it.

Q. And how do the solvents affect the rate of chemical reactions in the bulk solution in a pre-lyophilization solution?

A. Okay. So the solvents interact with solute material. And different solvents can interact with the same solute

material differently. But also the same solvent can interact with different solute materials differently.

Of course, during a chemical reaction, when something is changing from being one material into another material, you have changing solute. So you have to consider not only the differences of the solvents that you might use but the differences of the solutes that you might have.

So in the end, you are kind of considering the differences of the differences.

Q. And how do these differences in the interactions between solvents and solutes, like polar interactions or hydrogen bonding, affect the rate of a chemical reaction?

A. So there are a myriad of potential ways in which a solvent can interact with a solute material, which are what we umbrella call polarity. Polarity isn't just one thing. It's lots and lots and lots of things.

So those interactions can stabilize the different species that are present in the solution differently. And those differences then lead to differences particularly in rates of reactions.

Q. I want to turn a little bit to what reactions are. What is a chemical reaction?

A. So a chemical reaction is where one or more chemicals transforms into another one.

Q. If we put up PDX-9-8, have you created a slide to help

explain some of the basic reaction types?
A. I have, indeed.
So what you can see listed on the left-hand side of the screen are the things that we call starting materials or sometimes I will use the word reactants, I imagine.
On the right-hand side of the screen, you have the things that we call products, the products that are produced in the reaction, they are the products.
At the top we have the simplest kind of reaction one can conceptualize, which is a simple addition. So something adds to something else to make the product. The reverse of that reaction is the elimination, so you have a molecule now come apart and produce two separate molecules. And importantly for this case, at the bottom there is a thing called a substitution, in which something is added to the molecule and something else is removed from the molecule, a thing we call "leaving group."
Q. What is a reaction mechanism?
A. So this very simplified picture gives you the beginning of the process and the end of the process. Of course, there is a pathway to get from the beginning to the end. And the reaction mechanism is the thing that describes that pathway.
Q. Is understanding that reaction mechanism relevant to understanding how a solvent would affect a reaction?

:17:35 A. **You can't understand how a solvent will affect a**
:17:37 **reaction without understanding the reaction mechanism.**
:17:41 Q. **Why not?**
:17:41 A. **Because these different species are formed along the**
:17:46 **way, along the pathway, the solvent can interact with all of**
:17:49 **these and does interact with all of these. So if you don't**
:17:53 **know they are there or you don't know the right ones, then**
:17:56 **you can't make any predictions at all.**
:17:57 Q. **So I want to talk, then, Dr. Welton, about a**
:18:02 **particular chemical reaction that the Court has heard a fair**
:18:05 **amount about, hydrolysis.**
:18:07 A. **Yes.**
:18:07 Q. **What is hydrolysis?**
:18:08 A. **So hydrolysis is a type of nucleophilic substitution**
:18:14 **in which water is one of the reagents of the reaction.**
:18:18 Q. **And if we pull up PDX-9-9. Have you created an**
:18:24 **animation to describe what a nucleophilic substitution**
:18:27 **reaction is?**
:18:28 A. **Yes. Here is my generic of a nucleophilic**
:18:31 **substitution. You heard the word nucleophile I think on**
:18:34 **Tuesday. Nucleophile, literally, nucleus, positive loving,**
:18:39 **and so it is trying to seek out a positive charge. And it**
:18:43 **will find that where we have this electrophile, so the**
:18:47 **electrophile is the reverse, it's looking for electron, it's**
:18:52 **looking for a negative charge.**

:18:54 **And the leading group will then leave. This is**
:18:57 **animated. So you can see, there you have your very simple**
:19:01 **idea of a nucleophilic substitution.**
:19:06 Q. **Have you created an animation to show specifically the**
:19:10 **nucleophilic substitution reaction of hydrolysis?**
:19:12 A. **I have, indeed.**
:19:13 Q. **If we can pull up PDX-9-10. Can you describe for the**
:19:19 **Court the nucleophilic substitution reaction of hydrolysis?**
:19:22 A. **So in hydrolysis, water is acting as the nucleophile.**
:19:26 **So the water has to come and react with the electrophile,**
:19:30 **and the leaving group has to leave.**
:19:36 Q. **If we can run the animation, what does that show?**
:19:40 A. **That shows the water coming into the electrophile and**
:19:43 **the leaving group leaving.**
:19:45 Q. **What are some of the most well-known nucleophilic**
:19:49 **substitution reaction mechanisms?**
:19:51 A. **So there are two broad classes of nucleophilic**
:19:56 **substitution, the SN1 reaction and the SN2 reaction. There**
:20:02 **are two subgroups of the SN1 and there are four subgroups of**
:20:07 **the SN2, but I shall not be going into that level of detail.**
:20:11 **I should point out that each of those subgroups does have**
:20:15 **different solvent effects in them.**
:20:17 Q. **I want to stay away from the subgroups. Have you also**
:20:19 **prepared some slides to help explain SN1 versus SN2?**
:20:24 A. **I have, indeed.**

:20:24 Q. **If we could have PDX-9-11. Before we start the**
:20:29 **animation, could you just describe for the Court what we see**
:20:32 **here on the screen?**
:20:33 A. **So what I have shown on the screen here is a generic**
:20:37 **molecule. We have a carbon, that's the C, and the carbon is**
:20:41 **attached to the leaving group. And this is the molecule**
:20:44 **that the reaction is about to occur to.**
:20:48 **In an SN1, a unimolecular, that means**
:20:53 **one-molecule-involved reaction, first, the leaving group has**
:20:56 **to leave. In leaving, the leaving group makes a space so**
:21:00 **the nucleophile can then subsequently come in and form the**
:21:04 **new chemical bond.**
:21:06 **So this reaction happens in two distinct**
:21:08 **separate steps.**
:21:09 Q. **And is an SN2 reaction different in some way?**
:21:15 A. **Definitely. It is a concerted reaction. I have**
:21:18 **generated another graphic.**
:21:19 Q. **If we could have PDX-9-12.**
:21:24 A. **A concerted reaction is a simultaneous reaction. So**
:21:28 **now you have the same molecule. And you have your -- not**
:21:32 **the same, it wouldn't be the same molecule. You have the**
:21:35 **same generic. You have your carbon and your leaving group.**
:21:38 **But instead of the leaving group leaving first, what happens**
:21:42 **is that the nucleophile arrives as the leaving group is**
:21:47 **leaving.**

:21:47 So, as I say, it's a concerted simultaneous
:21:51 process that only occurs in one step.
:21:55 Q. Just to make sure I have got it right, an SN1 reaction
:21:58 has two steps and an SN2 reaction has one step?
:22:04 A. Indeed, that's correct.
:22:05 Q. What's generally known in the art about the solvent
:22:10 effects for SN1 and SN2 reaction?
:22:14 A. The solvent effects on these reactions are the most
:22:16 well-established solvent effects in the art. Christopher
:22:23 Ingold, in the 1930s, initiated a study in this area. So
:22:28 SN1 and SN2 reactions are extremely well known.
:22:31 Q. Based on your experience and in your opinion, sir, are
:22:35 solvent effects reaction-mechanism-dependent?
:22:38 A. Completely.
:22:39 Q. Are there any other general types of nucleophilic
:22:43 substitution reactions that are going to be relevant to this
:22:46 case?
:22:46 A. So there is a specific kind of nucleophilic
:22:50 substitution reaction that is of importance in this case.
:22:54 That is the type of nucleophilic substitution that we call
:22:59 one with neighboring group participation.
:23:01 The two reactions I have described to you so far
:23:04 are reactions between different molecules, they are
:23:09 intermolecular.
:23:11 The neighboring group participation reaction has

a first part, which is intramolecular, that is within the same molecule.

I have generated a graphic.

Q. We will jump to that one in a minute, if we can hold off on that. I want to just talk briefly about -- let me back up.

Bendamustine has a neighboring group participation for its hydrolysis reaction?

A. That's correct, yes.

Q. Before we get to the bendamustine specifically, I just want to ask you a couple questions about mixtures of solvents. Is it possible to have a mixture of solvents together?

A. Yes, it is.

Q. And how does mixing solvents together affect the solvent effects?

A. So it becomes quite complex. So one might imagine that if you took two different liquids, A and B, and you mixed them in 50-50 mixture, that the properties of the mixture would be halfway between those of A and B.

But that's almost never the case, because to have that, you would require a thing that we call ideal mixing. And ideal mixing is in fact extremely rare. So you can't say I have got 50 percent of this and 50 percent of this so it will be halfway between those, or 75-25 and so

:24:29 on. You just can't say that.
:24:31 Q. What is the concept of preferential solvation?
:24:36 A. So I was talking about ideal mixing just with the
:24:39 mixing of A an B, two solvents. Of course, now you dissolve
:24:42 something in. Remember I said we had this environment which
:24:46 is generated by the molecules of the solvent. Again, at
:24:49 50-50, you might imagine that half of the molecules, half of
:24:54 the solvent molecules around a solute molecule would be one
:24:58 of them and half the other. That again is almost never the
:25:01 case, because the solute will have a preference for one of
:25:06 those solvent molecules. So you will ended you up with an
:25:10 off-50 preferential solvation. Without studying it you
:25:16 can't tell whether it's slightly off, a lot off. It's quite
:25:20 complex.
:25:22 Q. Thanks.
:25:23 Now I want to turn to bendamustine issues in
:25:26 particular, if we can.
:25:28 We have prepared a slide. If you could also
:25:30 look at JTX-1, the '190 patent, Column 1, Lines 40 to 50.
:25:35 It is PDX-9-13.
:25:43 A. Okay.
:25:56 Q. What is this structure?
:26:09 A. So this is the compound we've been talking about.
:26:12 This is bendamustine hydrochloride. The hydrochloride is
:26:15 the dot HCl that you see on the right-hand side. The

bendamustine is the big bit on the left-hand side.

And bendamustine has two functional groups. The mustard functional group on the far left. So you've been hearing the term nitrogen mustard. So a nitrogen mustard is a compound that has this particular structure within it.

So you have a nitrogen and there are two arms, and the two arms come out, and at the end of those arms there are chlorines. And you need to have that two-arm effect, two arms for something to be a mustard.

Q. And, Dr. Welton, was this structure of bendamustine known in the prior art before the Brittain patent?

A. Oh, yes.

Q. And are nitrogen mustards generally known as reactive compounds?

A. Yes. They're generally considered to be reactive compounds. But you do have to understand, that's a relative statement and context specific. There isn't a thing called reactive.

Q. And were nitrogen mustards known to be subject to degradation by hydrolysis?

A. They were, indeed, yes.

Q. I want to turn then to the Maas paper. I believe it's DTX-577 in your binder.

MR. WIESEN: And, your Honor, I'm going to note

:27:38 **for the record, there are two versions of the Maas paper,**
:27:42 **577 I believe and 146. The Maas paper, you'll recall, was**
:27:46 **in German.**
:27:48 **THE COURT: Yes.**
:27:50 **MR. WIESEN: There are two different**
:27:52 **translations. I don't believe that there are any issues**
:27:53 **left in the case that concern the translation, but different**
:27:56 **experts had considered different versions. We've managed to**
:27:59 **eliminate the dispute that might have come from that.**
:28:01 **THE COURT: Sure.**
:28:02 **MR. WIESEN: And I think that the version in**
:28:04 **this binder, if we did it right, is 577.**
:28:12 **BY MR. WIESEN:**
:28:13 Q. **Are you familiar with the Maas paper, sir?**
:28:14 A. **I am familiar with the paper.**
:28:15 Q. **And if you turn to Page 2, is there a diagram there?**
:28:22 **And we'll pull up PDX-9-14.**
:28:26 A. **Yes. This diagram is a representation of the, the**
:28:33 **hydrolysis of a generic mustard, nitrogen mustard.**
:28:38 Q. **And so just to be clear, the Maas paper describes the**
:28:43 **mechanism for hydrolysis for a mustard; is that correct?**
:28:48 A. **Yes.**
:28:49 Q. **All right. And have you created some, let's call it**
:28:54 **better looking animations to explain the reaction mechanisms**
:28:58 **for a nitrogen mustard to the Court?**

:29:00 A. **I have, sir, yes.**

:29:02 Q. **So let's turn to PDX-9-15. And can you describe for the Court how the bendamustine hydrochloride reaction mechanism for hydrolysis would work?**

:29:17 A. **So as I said, the mustard group is the part on the far left here, the nitrogen, the two arms and the chlorine.**

:29:25 **And, first of all, what happens is that the nitrogen interacts with the carbon onto which the chlorine is based, so the chlorine can now leave and the nitrogen is the thing that's substituting for it. And this is what is the neighboring group effect.**

:29:44 **So the nitrogen is the neighboring group in this intramolecular reaction generating the chloride ion, and they're the triangle you see is something that we call an aziridinium ion.**

:30:02 Q. **And what are the corners of the triangle in that in the aziridinium ion?**

:30:07 A. **They're the carbons in the chain of the mustard arm.**

:30:13 Q. **And is there a second step in the hydrolysis reaction mechanism for bendamustine hydrochloride?**

:30:17 A. **There is. We have not yet got water in it.**

:30:21 Q. **All right.**

:30:21 A. **So now what happens is the water comes and attacks the carbon on the apex of the triangle there to complete the**

reaction and give our hydrolysis.

Q. And is there a name we've been using for the resulting compound in this case?

A. This is the compound that people have been calling HP1.

Q. And so I may have asked this before, but is this an SN1 reaction or an SN2 reaction?

A. It's neither. It has composed of both, but it's neither.

So the SN1, we just needed the leading group to leave without any kind of interaction with the carbon, to make that open. We didn't have that open. So it was an internal reaction that was a little bit more like the, what we saw for the SN2 even though it was a intramolecular reaction because it only involves one molecule.

Then you have the second step to complete the hydrolysis, which is more -- again, kind of SN2 like because the nitrogen now becomes the leaving group and the water comes in, and so it's a bit like the mechanism for the SN2. It's much more like the mechanism for SN2, but it still has that intramolecular part.

Q. What was generally known in the art about the solvent effects on neighboring group participation reactions?

A. Almost nothing.

Q. And did you look through the index of your book to see

:32:09 **if there were any discussions about that that a person of**
:32:12 **ordinary skill in the art would know about?**
:32:13 A. **I did, and I took the PDF and scanned it. There were**
:32:20 **no neighboring group hydrolysis reactions in the book or**
:32:28 **indeed substitutions.**
:32:30 Q. **Now, just to be clear for the Court, when the**
:32:34 **hydrolysis reaction happens in bendamustine hydrochloride,**
:32:37 **what does the OH group replace in the bendamustine?**
:32:40 A. **So the OH replaces the chlorine.**
:32:45 Q. **Now, when were looking at the Maas paper before, and I**
:32:50 **want to go back a little bit to DTX-577. I think you had**
:32:55 **said that diagram in Maas was not specifically about**
:32:59 **bendamustine, it was about a more general compound or**
:33:02 **structure.**
:33:02 A. **Yes.**
:33:03 Q. **What type of structure was it talking about?**
:33:05 A. **So it was talking about a mustard. So I used the**
:33:08 **phrase functional group. Functional group essentially for a**
:33:13 **chemist means the business end of the molecule. And it's**
:33:17 **quite common when drawing a mechanism to just take the rest**
:33:21 **of the molecule and substitute a complex function with the**
:33:26 **letter "R," so that's the "R" that we see here. This is not**
:33:29 **specific to any particular one compound. It is something**
:33:33 **that she's representing for a generic mustard.**
:33:36 Q. **And if we turn in your binder to DTX-577, the Maas**

:33:44 paper, and we look on the first page in the paragraph under
:33:48 studies and results. If we could pull that up. If we could
:33:59 blow up the paragraph under two.
:34:04 MR. WIESEN: And this is the translation,
:34:05 your Honor, that we're using, I think, from the prosecution
:34:08 history.
:34:09 BY MR. WIESEN:
:34:10 Q. Does Maas discuss general types of structures that
:34:12 have this same reaction mechanism?
:34:15 A. Yes. The mustards.
:34:18 Q. And what does she say about how --
:34:22 THE COURT: Yes?
:34:22 MR. DAIGNAULT: Your Honor, I just want to note
:34:24 for the record that Dr. Welton did not discuss melphalan,
:34:29 and did not discuss this in his expert report.
:34:32 MR. WIESEN: Your Honor, he did generally
:34:33 discuss this paragraph and passage in Maas. We're trying to
:34:36 avoid talking about melphalan in particular and just talk
:34:40 generally about the mustards.
:34:41 THE COURT: Mr. Daignault?
:34:43 MR. DAIGNAULT: I will see how it progresses. I
:34:46 just want to note that for the record.
:34:47 THE COURT: All right. You're withdrawing your
:34:49 objection for now?
:34:49 MR. DAIGNAULT: My objection I think we'll

see how the witness testifies, your Honor. But we are objecting --

THE COURT: You just want to put me on notice?

MR. DAIGNAULT: And we're objecting to any testimony about melphalan.

THE COURT: That's not --

MR. WIESEN: I'm going to try to stay a general level above melphalan.

THE COURT: Let's see if you can succeed.

BY MR. WIESEN:

Q. Does Maas make any suggestions about whether one can learn something from the structural similarities of one compound to another for reaction mechanisms?

A. Yes, she does.

Q. What does she teach here in this paragraph under two, without talking about a particular compound?

MR. DAIGNAULT: Objection, your Honor. This discussion is not in his expert report. The chemical structures and how they relate to the reactions, they're disclosed in Maas. The discussion in his report is two paragraphs.

THE COURT: You're saying this --

MR. DAIGNAULT: This subject --

THE COURT: This subject --

MR. DAIGNAULT: This subject that Dr. Welton is

about to discuss is not in his expert report.

THE COURT: Why don't you and your colleagues have a conference there.

MR. WIESEN: May we have a minute, your Honor?

(Pause while counsel conferred.)

MR. WIESEN: Your Honor, apparently, we have a dispute about this issue.

THE COURT: All right. Let's discuss it at sidebar for a moment.

(Sidebar conference held as follows.)

THE COURT: Could we have the question read back?

(The Court Reporter read back the pending question as follows:

"Question: What does she teach here in this paragraph under two, without talking about a particular compound?")

THE COURT: All right. We have the question in mind.

MR. DAIGNAULT: So, your Honor, the only particular compound --

THE COURT: You can speak up.

MR. DAIGNAULT: The only particular compound, the only thing that has been discussed in these two paragraphs is the general proposition about nitrogen

mustards in general. He does not go into the different chemical compounds that are mentioned in Maas.

THE COURT: In Maas.

MR. DAIGNAULT: In fact, your Honor, they cite to pages in Maas, but this is two pages of text. He doesn't point out what he's talking about.

So this is, again, a very, very general discussion, the kind of discussion has already been given about nitrogen mustards in general, but he's not then moving that discussion to specific compounds that are disclosed in Maas like melphalan and the others. So this is beyond the scope of his report.

THE COURT: All right.

MR. WIESEN: Your Honor, we're trying to address that. What -- the expert report with Dr. Welton discusses in paragraph 24, he cites specifically the Maas reference. He cites specifically the page that has the discussion, and he talks specifically about nitrogen mustards generally being deprotonated. That's the subject he's talking about. She talks about nitrogen mustards having reactions an learning one thing from another in nitrogen mustards.

We're trying to keep it talk about the structures and keep it at the high level based on that citation.

THE COURT: I'm going to let him keep it at the

high level. I don't think you object to that.

MR. DAIGNAULT: No.

THE COURT: Okay.

MR. DAIGNAULT: Not the high level.

MR. WIESEN: This is pretty much maybe one more question in this area.

MR. DAIGNAULT: That's fine.

THE COURT: All right.

MR. DAIGNAULT: Your Honor, what was not in the report is, so here are the two pages in Maas.

THE COURT: Well, why don't you rise if you don't think he's sufficiently high.

MR. DAIGNAULT: Right. Okay.

THE COURT: Let us know.

MR. DAIGNAULT: So keep it high.

MR. WIESEN: I will try.

(End of sidebar conference.)

THE COURT: We will have these interruptions from time to time, Doctor. I apologize.

THE WITNESS: It's not your fault.

BY MR. WIESEN:

Q. If we could put that paragraph of Maas back up on the screen, please, from DTX-577. Dr. Welton, without talking about any particular compounds, is there a class of compounds that the Maas paper is talking about?

:39:55 A. **Yes, there is.**

:39:57 Q. **What is that class?**

:39:59 A. **The nitrogen mustards.**

:40:01 Q. **Why does Maas specifically talk about nitrogen mustards as a class in this discussion?**

:40:07 A. **So remember I used the phrase functional group. So functional groups are reaction centers within molecules. So although it's never guaranteed, you can view molecules that have the same functional group as being likely to have similar reactivities.**

:40:30 **So the mustard, the nitrogen mustard is a functional group. So other compounds that are nitrogen mustards might, not certainly will, might have the same reactivity as the other nitrogen mustards.**

:40:46 Q. **In your study of solvent effects, sir, do you generally agree with that concept of the same functional groups?**

:40:54 A. **It's first-year chemistry. Yes.**

:40:55 Q. **Now, if the degradation pathway were different, either had different functional groups or just a different reaction mechanism, what would you learn from one compound about the solvent effects on another compound?**

:41:07 A. **So if compounds don't have the same functional groups, they will have different reactivities. But, also, as well as being the place where reactions happen, functional groups**

are the place in the molecules where interactions happen with neighboring materials.

So different functional groups will lead to different solvent effects, particularly the specific effects of things like hydrogen bonding, very important in the solvent effects.

Q. We have been very focused on the nitrogen mustard functional group and the hydrolysis reaction. Is there another functional group in bendamustine hydrochloride?

A. There is, indeed.

Q. If we could put up PDX-9-20.

A. At the other end of the molecule there is a carboxylic acid group.

Q. Just very generally, what is that?

A. So you can see here, I have shown you, there were two oxygens. One of those oxygens is bonded to a hydrogen atom, really a proton. Between them there is a carbon, which the carboxylic acid group is then attached to, if you like, the R of the molecule.

Q. And is there a different reaction mechanism for the carboxylic acid than there is for the nitrogen mustard?

MR. DAIGNAULT: Again, Your Honor, not in his expert report.

MR. WIESEN: That is the only question on the subject, Your Honor.

:42:37 **MR. DAIGNAULT: It is not in his expert report.**
:42:39 **It may be one more question, but it's not in his expert**
:42:41 **report.**
:42:42 **THE COURT: That's fair comment, Mr. Daignault.**
:42:44 **MR. WIESEN: Your Honor, he talks generally**
:42:47 **about structures. The bendamustine ethanol ester you have**
:42:50 **heard so much about happens at that side and location of the**
:42:54 **molecule. It's simply so that that explanation can be given**
:42:57 **from a chemical description by a chemist so that the Court**
:43:00 **can understand how the things happen that you have been**
:43:03 **hearing about for the last week.**
:43:05 **THE COURT: All right. I am going to allow it.**
:43:12 **THE WITNESS: Am I answering?**
:43:13 **THE COURT: Yes, sir.**
:43:16 **THE WITNESS: So, no, not only the mechanisms of**
:43:19 **the reactions but the actual reactions that take place will**
:43:23 **be different on the carboxylic acid than on the nitrogen**
:43:28 **mustard side of the molecule.**
:43:29 **BY MR. WIESEN:**
:43:31 Q. **I want to move on to more of the substance of your**
:43:37 **opinions and looking at some of the specific references that**
:43:41 **the defendants have talked about.**
:43:43 **If we could pull up PDX-R-22.**
:43:59 **As I said earlier, sir, we are going limit the**
:44:01 **testimony to just the effects of TBA in a pre-lyophilization**

:44:07 **solution.**

:44:09 **First we are going to talk about three**
:44:11 **references that I think Dr. Kwan and Dr. Kamat talked about,**
:44:14 **the Ni paper, the Teagarden paper, and Baldi paper, that do**
:44:19 **use TBA, and we will look at the compounds there.**
:44:24 **Did you hear Dr. Kamat and Kwan testify it would**
:44:27 **have been obvious to a person of ordinary skill in the art**
:44:29 **as of 2005 to decrease the hydrolysis degradation in the**
:44:35 **Ribomustin bulk solution by using TBA and water as a solvent**
:44:40 **system?**
:44:40 A. **I did hear them say that.**
:44:41 Q. **Do you agree with that?**
:44:43 A. **No, I don't.**
:44:43 Q. **Why not?**
:44:46 A. **So here is a summary of the prior art papers**
:44:50 **distributed in terms of the similarity of the molecular**
:44:54 **structures of the compounds being discussed and the solvent**
:44:59 **systems that we used with them.**
:45:01 **So the Ni paper, the Teagarden paper, and the**
:45:06 **Baldi paper discuss compounds that have dissimilar**
:45:09 **structures to bendamustine and do use TBA, the references**
:45:15 **that discuss similar compounds but do not use TBA, so the**
:45:22 **references with similar compounds do not use TBA, and the**
:45:25 **references that actually use the material we are talking**
:45:28 **about, we are talking about itself, bendamustine, also do**

:45:32 not use TBA.

:45:36 Q. All right, sir. In your opinion, if a person of

:45:39 ordinary skill in the art were worried and focused only on

:45:44 reducing or eliminating hydrolysis of bendamustine

:45:48 hydrochloride, what's the first thing they would do in

:45:51 choosing a solvent?

:45:53 A. They would take away the water. So you would use an

:45:56 anhydrous, without water, anhydrous solvent, because the

:46:03 reaction is with water. And so if you want to prevent the

:46:07 reaction with water, you exclude the water.

:46:10 Q. Have you seen any references that lyophilize

:46:18 bendamustine from a pre-lyophilization solution that is

:46:21 anhydrous, has no water?

:46:23 A. No.

:46:23 Q. If, contrary to your opinion that a person might think

:46:33 about using an anhydrous solution, a person of ordinary

:46:37 skill in the art decided to use some sort of a water-organic

:46:42 solvent mixture in the bulk solution, would any of these

:46:44 three references, in your opinion, Ni, Teagarden, or Baldi,

:46:50 help a person of ordinary skill in the art in selecting the

:46:54 solvent mixture to use for bendamustine hydrochloride in

:46:56 particular?

:46:57 A. No, not at all.

:47:02 Q. Let's start by taking a look at these references. I

:47:14 want to turn to JTX-79, which is, I believe, the Ni paper.

:47:20 **If we can call up PDX-9-24, I believe. Are you familiar**
:47:32 **with this paper, sir?**
:47:33 A. **I am, indeed, yes.**
:47:34 Q. **Did you hear testimony concerning the Ni paper?**
:47:37 A. **Yes, I did.**
:47:39 Q. **How many compounds does Dr. Ni study in this paper?**
:47:43 A. **One.**
:47:44 Q. **And if we can turn to PDX-9-25, what is that compound?**
:47:56 A. **So let's call it SarCNU. It is a nitrosourea**
:48:03 **compound. So the nitrosourea is, in the center of this**
:48:07 **compound you can see the oxygens, three nitrogens and then**
:48:11 **another oxygen joined with an equal sign, that means a**
:48:14 **double bond. That central block is the thing that**
:48:19 **determines this to be a nitrosourea.**
:48:24 Q. **Is this a nitrogen mustard?**
:48:26 A. **No, it is not.**
:48:26 Q. **Why not?**
:48:27 A. **Because it doesn't have the double arm on the**
:48:30 **nitrogen, that nitrogen mustards have.**
:48:33 Q. **Were you here for Dr. Kamat's testimony, sir?**
:48:37 A. **Yes, I was.**
:48:38 Q. **And did you hear during cross-examination his**
:48:41 **explanation of how he understood SarCNU degraded by**
:48:46 **hydrolysis, the reaction mechanism?**
:48:48 A. **I did hear him say that, yes.**

:48:51 Q. **Did you hear him testify that a person of ordinary**
:48:54 **skill in the art would believe that SarCNU would degrade by**
:48:58 **hydrolysis in the same way as bendamustine hydrochloride**
:49:02 **with the water coming in at the chloride ion on the left**
:49:05 **side of the molecule?**
:49:06 A. **I did hear him say that, yes.**
:49:08 Q. **Do you agree with Dr. Kamat concerning that?**
:49:11 A. **No. He was mistaken.**
:49:12 Q. **And how do you know that?**
:49:15 A. **Because there is another Ni reference, her thesis,**
:49:19 **that tells you what the mechanism is. And it's not that**
:49:25 **mechanism, and the chlorine is not eliminated during any**
:49:30 **process of that decomposition.**
:49:31 Q. **Let's go to PTX-500 in your binder. If we pull up**
:49:50 **Slide PDX-9-26, what is this document, sir?**
:49:57 A. **This is Ni's thesis.**
:50:00 Q. **What is the date on it?**
:50:02 A. **2002.**
:50:03 Q. **That is before 2005?**
:50:05 A. **Yes.**
:50:06 **MR. DAIGNAULT: Your Honor, I am informed that**
:50:08 **this was not in his expert report.**
:50:09 **MR. WIESEN: Can I have a moment, Your Honor?**
:50:18 **THE COURT: Yes, you may.**
:50:20 **MR. WIESEN: I believe we found it.**

:50:21 **MR. DAIGNAULT: Withdrawn, Your Honor.**

:50:25 **THE COURT: You are right. It's not my fault.**

:50:27 **(Laughter.)**

:50:29 **THE COURT: Go ahead.**

:50:30 **BY MR. WIESEN:**

:50:30 Q. **If we could turn to Page 77 of the thesis, have you helped us create a slide that highlights --**

:50:39 A. **I have, indeed.**

:50:40 Q. **If we could pull up PDX-9-27, what does Dr. Ni's thesis show about the degradation mechanism of SarCNU in water?**

:50:50 A. **So I have circled the chlorine atom for you so you can see it clearly. And I have also highlighted a carbon, and that carbon is the center at which the reaction is going to finish.**

:51:04 **So as we move right across the screen, you can see that the water molecule comes in fact nowhere near the chlorine. It comes in in the nitrosourea part of the molecule. The water then reacts with the nitrosourea part, splitting it apart. And you can see the left-hand side of the product, the chlorine is still quite clearly attached to the molecule. And then there is the other part of the molecule.**

:51:34 **So it's not just that it has a different reaction mechanism. It is a different reaction.**

:51:40 Q. **There is a laser pointer, I believe.**
:51:44 A. **I am sorry.**
:51:44 Q. **If you need it, Dr. Welton.**
:51:46 A. **I am so used to gesticulating.**
:51:53 Q. **The court reporter can't record the gesticulation.**
:51:57 **Does Ni hypothesize in her dissertation that we might need to look at another potential reaction for hydrolysis?**
:52:05 A. **There is another one, yes.**
:52:06 Q. **Does it have the same general effect that it is not at the chlorine molecule?**
:52:11 A. **It is not at the chlorine.**
:52:13 Q. **If we turn back then to JTX-79, the Ni paper itself, does Ni conclude that SarCNU should be lyophilized from a co-solvent mixture of water and TBA?**
:52:34 A. **Oh, no, not at all. She prefers pure TBA. That is, anhydrous, water-free TBA.**
:52:44 Q. **Did she study the effect of adding water for the pre-lyophilized solution on the stability of SarCNU?**
:52:54 A. **Yes, she did.**
:52:56 Q. **If we could have Slide 9-28. What does Figure 4 of the Ni paper, JTX-79, show?**
:53:02 A. **So this is the degradation of the SarCNU under various different conditions of water, TBA, or water-TBA mixtures with time.**

:53:17 Q. **And I notice on the y axis it says log percent**
:53:21 **remaining. What does it mean that this is on a log scale?**
:53:25 A. **So rather than being a numerical -- a straightforward**
:53:29 **arithmetic one, two, three scale, here, this is a scale, a**
:53:35 **log scale, she hasn't defined it, but I think she means**
:53:39 **natural log, because that's how you normally analyze**
:53:43 **kinetics, so each unit's differentiation is the power -- it**
:53:48 **tells you the power to which a number called E is raised in**
:53:52 **order to represent the actual number.**
:53:58 Q. **If it weren't on a log scale would these differences**
:54:02 **look even larger?**
:54:03 A. **If it wasn't on a log scale, not only would they look**
:54:08 **bigger differences, but they wouldn't be straight lines. So**
:54:10 **the use of the log scale is to provide a mathematical tool**
:54:15 **to generate the straight line, which you can then analyze**
:54:18 **more simply.**
:54:33 Q. **Dr. Welton, in light of what a person of ordinary**
:54:46 **skill in the art would know about the different reaction**
:54:49 **mechanisms by, for hydrolysis for SarCNU as studied in Ni**
:54:56 **and bendamustine hydrochloride, what in your opinion would a**
:54:58 **person of ordinary skill in the art take away from the Ni**
:55:01 **paper, JTX-79, concerning whether t-butanol would slow down**
:55:05 **the degradation by hydrolysis of bendamustine?**
:55:08 A. **Nothing. The reaction is different and it would be**
:55:13 **different.**

:55:13 Q. **And, Dr. Welton, I want to just take a quick aside.**
:55:18 **If you could turn to JTX-6, the '863 patent in your**
:55:20 **binder.**
:55:22 A. **JTX-6? Yes.**
:55:27 Q. **And if we turn to the second page. What's your**
:55:37 **understanding of what this list is on the front of the**
:55:39 **patent?**
:55:39 A. **This is the list of publications that were submitted**
:55:44 **as having been considered when writing the patent.**
:55:46 Q. **And did you find the Ni paper in this patent?**
:55:50 A. **I do. It's halfway down in the second column.**
:55:55 Q. **Thank you, Dr. Welton. I want to move to the next**
:56:03 **reference then, the Teagarden paper, if we can.**
:56:07 **Did you hear Dr. Kamat and Dr. Kwan spend some**
:56:11 **time talking about the Teagarden paper?**
:56:13 A. **I did, indeed, yes.**
:56:14 Q. **And if we could turn to -- DTX-999 I believe is the**
:56:20 **version that we're using.**
:56:22 A. **Yes.**
:56:22 Q. **Though I might be wrong about that.**
:56:25 A. **That's correct.**
:56:28 **MR. WIESEN: And, your Honor, this is the**
:56:30 **one I think we referred to previously. I think there**
:56:32 **are at least two versions of that. I will match it up after**
:56:36 **trial.**

:56:37 **BY MR. WIESEN:**

:56:39 **Q. Do you agree with the testimony from Dr. Kwan and Kamat, that the Teagarden references discussion of TBA stabilizing compounds in pre-lyophilization solution would lead a person of ordinary skill in the art to use TBA with bendamustine?**

:56:57 **A. No.**

:56:58 **Q. Why not?**

:56:59 **A. Because therefore isn't sufficient information. When we look at the, the references that are used in the Teagarden paper to compounds and their stability in mixed aqueous solution, TBA solution, none of these are compounds that have similar structures to bendamustine. They have different functional groups. They're not the same.**

:57:29 **Q. All right. If we turn to Page 117 of Teagarden, Section 3, the stabilization of bulk solutions.**

:57:39 **And I know we've got some call-out slides that we'll get to, but for the record, is that the section that you focused on?**

:57:44 **A. Yes, Section 3, yes.**

:57:46 **Q. And how many compounds are discussed in Section 3 of Teagarden, the stabilization of bulk solution?**

:57:51 **A. Three.**

:57:54 **MR. WIESEN: If we could have PDX-9-30.**

:57:59 **BY MR. WIESEN:**

:58:00 Q. **What does this show?**

:58:00 A. **So these are the three compounds in question. Carmustine, which is a nitrosourea. Alprostadil and trecetilide.**

:58:12 Q. **Let's start then with the discussion of carmustine in Teagarden. It's on that same page, 117 in the right-hand column.**

:58:25 **And do you see a chemical name written out there?**

:58:27 A. **Yes, I do.**

:58:28 Q. **And is that carmustine?**

:58:30 A. **That's carmustine.**

:58:32 Q. **What was is the co-solvent used as described in Teagarden for the carmustine compound?**

:58:39 A. **This is an ethanol/water solution.**

:58:40 Q. **Is there any disclosure of a TBA solution for carmustine?**

:58:45 A. **No, there isn't.**

:58:49 Q. **What does Teagarden disclose about whether they were successful in lyophilizing carmustine from an ethanol water solution?**

:58:56 A. **It didn't work.**

:58:57 Q. **And how do you know that?**

:58:58 A. **Unfortunately, freeze-drying the product in the ethanol/water.**

:59:06

:59:07 Q. **So what would the discussion of carmustine teach to a**
:59:11 **person of ordinary skill in the art about using TBA to slow**
:59:15 **down the degradation by hydrolysis of bendamustine**
:59:17 **hydrochloride in a --**
:59:20 A. **Absolutely nothing.**
:59:21 Q. **All right. Then let's turn to the second compound**
:59:27 **that's discussed in this section of Teagarden. If we can**
:59:37 **call up slide 9-32.**
:59:38 **What is the second compound that's discussed?**
:59:40 A. **So this is are alprostadil. It has been treated in a**
:59:46 **tert-butanol/water solution. However, you saw with the**
:59:51 **structures, it has a completely different structure, and, in**
:59:55 **fact, it's a first-order reaction. And one of the things**
:00:00 **that we know about bendamustine is it is a pseudo**
:00:03 **first-order reaction.**
:00:05 Q. **And without describing what a first order versus**
:00:08 **pseudo first order reaction is, what would that tell you**
:00:13 **about whether the reaction mechanisms are the same or**
:00:15 **different for alprostadil and bendamustine hydrochloride?**
:00:21 A. **There isn't.**
:00:22 Q. **Is alprostadil a nitrogen mustard?**
:00:25 A. **No, it is not.**
:00:26 Q. **And if we turn to the next slide, PDX-9-33, what do we**
:00:31 **have here?**
:00:31 A. **That's alprostadil.**

:00:34 Q. **And does alprostadil -- is it possible that**
:00:37 **alprostadil could degrade by hydrolysis as an azrididinium**
:00:43 **ion and neighboring group participation?**
:00:45 A. **No. Well, there's no chlorine and there's no**
:00:47 **nitrogen.**
:00:49 Q. **Does Teagarden disclose the mechanism by which**
:00:52 **alprostadil degrades by hydrolysis?**
:00:54 A. **No, it doesn't.**
:00:55 Q. **In your opinion, sir, what motivation would**
:01:04 **Teagarden's discussion about alprostadil provide to a person**
:01:06 **of ordinary skill in the art concerning the idea to use TBA**
:01:11 **in water as a co-solvent system in the pre-lyophilization**
:01:15 **system of bendamustine?**
:01:16 A. **Nothing.**
:01:16 Q. **All right. Then let's turn to the third compound**
:01:22 **discussed in Section 3 of the Teagarden reference. This is**
:01:25 **on Page 118 of the paper, for the record, DTX-999. What**
:01:35 **compound is discussed, sir?**
:01:36 A. **This is trecetilide.**
:01:40 Q. **And what was the co-solvent system used?**
:01:41 A. **This time it is in a tert-butanol/water mixture.**
:01:46 Q. **And if we turn to the next slide, PDX-9-35, what does**
:01:52 **this show?**
:01:53 A. **This is trecetilide.**
:01:56 Q. **And is trecetilide a nitrogen mustard?**

:01:59 A. **No.**

:02:00 Q. **Does trecetilide degrade by hydrolysis, by the same**
:02:04 **mechanism of bendamustine?**

:02:05 A. **No, it does not.**

:02:06 Q. **And if we go back to the Teagarden paper itself on**
:02:10 **Page 118 on the left-hand side, if we call up PDX-9-36, does**
:02:18 **Teagarden actually talk about the reaction mechanism for**
:02:22 **hydrolysis of trecetilide?**

:02:23 A. **Oh, yes. It tells us what they are.**

:02:26 Q. **And what are they?**

:02:27 A. **So, first of all, there are two of them. So there's**
:02:31 **an SN1 substitution that we demonstrated earlier, but then**
:02:34 **there's also an elimination, so there's, in fact, two**
:02:37 **reactions occurring, two mechanisms occurring to**
:02:40 **defluorinate a compound in the presence of water.**

:02:45 Q. **And Teagarden specifically talks about the degradation**
:02:50 **reaction mechanism; is that right?**

:02:52 A. **Yes.**

:02:57 Q. **And what would a person of ordinary skill in the art**
:03:00 **understand about why Teagarden talks about reaction**
:03:02 **mechanisms for trecetilide?**

:03:05 A. **Well, because as I've explained, reaction mechanisms**
:03:07 **are vital to understanding the effect.**

:03:10 Q. **And why does this different reaction mechanism for**
:01:54 **trecetilide that Teagarden discloses, what would the**

:03:20 **discussion of the stabilization of trecetilide fumarate in**
:03:24 **the pre-lyophilization solution with TBA teach to a person**
:03:27 **of ordinary skill in the art about whether TBA would**
:03:32 **stabilize bendamustine hydrochloride and reduce the**
:03:36 **hydrolysis?**
:03:37 A. **Nothing.**
:03:38 Q. **Sir, you've reviewed the entirety of the Teagarden**
:03:46 **paper?**
:03:47 A. **I have, yes.**
:03:49 Q. **And does Teagarden talk about any other compound**
:03:54 **specifically being stabilized in the pre-lyophilization**
:03:57 **solution by the inclusion of TBA?**
:04:00 A. **No. Just, well, just those two.**
:04:02 Q. **And based on the detail then in Section 3 of**
:04:06 **Teagarden, what would a person of ordinary skill in the art**
:04:09 **go take away from Teagarden concerning whether TBA would**
:04:13 **stabilize and reduce the hydrolysis of bendamustine**
:04:16 **hydrochloride?**
:04:17 A. **Nothing.**
:04:22 Q. **I want to look briefly at one other reference. I**
:04:25 **think we've heard a little bit about DTX-586, the Baldi**
:04:30 **paper, and that's PDX-9-38. Are you familiar with this**
:04:39 **paper, sir?**
:04:40 A. **I am familiar with it, yes.**
:04:43 Q. **And does Baldi talk about using TBA to stabilize or**

:04:49 **reduce the hydrolysis of any compound?**

:04:52 A. **No. That's not what this paper is about.**

:04:54 Q. **What is the paper about?**

:04:56 A. **This is about using a statistical procedure for optimizing the freeze-drying of the drug. Freeze-drying, lyophilizing.**

:05:08 Q. **And so would Baldi teach a person of ordinary skill in the art about whether TBA would help stabilize any compound?**

:05:15 A. **No.**

:05:15 Q. **In the pre-lyophilization solution that had water and TBA?**

:05:19 A. **No. It's on a different subject.**

:05:21 Q. **And, Dr. Welton, why is it important that the reaction mechanism for hydrolysis of the compounds and the references discussed by Dr. Kamat and Kwan are different than the reaction mechanism for bendamustine hydrochloride?**

:05:42 A. **Because you can't take the understanding, the effects on different reactions and different mechanisms to imply what the, the -- or predict what the effect will be on another reaction. They're just too different.**

:06:04 Q. **If we could go, then, to PDX-9-40, then we'll move on to the next topic in your testimony.**

:06:11 **So what is the next topic that you are going to talk about, sir?**

:06:17 A. **So now we're moving towards compounds that are more**
:06:21 **similar to bendamustine, and unfortunately though, these are**
:06:28 **found in references that do not use TBA.**
:06:08 Q. **If you will turn then to DTX-348, the Sauerbier**
:06:13 **patent. PDX-9-41. Thank you. Are you familiar with this**
:06:22 **reference?**
:06:23 A. **I am, indeed.**
:06:24 Q. **If we turn to Column 1, Lines 14 to 18, what compound**
:06:30 **is discussed here?**
:06:31 A. **So this is ifosfamide.**
:06:34 Q. **And what kind of compound is ifosfamide?**
:06:38 A. **Technically, ifosfamide is something we call a**
:06:41 **bis-half mustard. So superficially, you can see the two**
:06:44 **arms on the compound. So it's mustard-like. But they are**
:06:49 **actually on two separate nitrogens. So this you would call**
:06:52 **a bis-half mustard. Bis meaning two half-mustards.**
:06:56 Q. **And how would you expect this compound to degrade by**
:07:00 **hydrolysis?**
:07:02 A. **So you would have an expectation that this compound**
:07:04 **can take part in a neighboring group participation reaction.**
:07:10 Q. **If you could turn to Column 3, around Line 14 of**
:07:15 **Sauerbier, if we call up the next slide. What solution is**
:07:21 **used for the pre-lyophilization solution in Sauerbier of the**
:07:27 **compound ifosfamide?**
:07:29 A. **They use ethanol-water solutions.**

:07:31 Q. **So what would Sauerbier teach to a person of ordinary**
:07:35 **skill in the art about the pre-lyophilization solution to**
:07:39 **use for bendamustine hydrochloride?**
:07:42 A. **So it would give them a guide, not an instruction, it**
:07:46 **would give them a guide that there are available**
:07:48 **alternatives that might be successful.**
:07:51 Q. **From Sauerbier, would a person of ordinary skill in**
:07:57 **the art know that water and ethanol combined would work as a**
:08:01 **pre-lyophilization solution for bendamustine hydrochloride**
:08:04 **to stabilize it from hydrolysis?**
:08:06 A. **Oh, yes. That's what the patent claims.**
:08:10 Q. **Sorry, from Sauerbier, would they know that**
:08:13 **bendamustine hydrochloride would be stabilized?**
:08:17 A. **For Sauerbier, sorry. Nothing to do with bendamustine**
:08:21 **in Sauerbier, sorry.**
:08:23 Q. **Just to be clear, Sauerbier talks about ifosfamide,**
:08:27 **not bendamustine?**
:08:28 A. **Yes. Sorry.**
:08:28 Q. **Then let's turn to the next reference, DTX-349, the**
:08:38 **Alexander patent. Are you familiar with that as well?**
:08:40 A. **I am, indeed.**
:08:41 Q. **And what does that disclose, if we turn to the next**
:08:47 **slide?**
:08:48 A. **So this is a lyophilization of cyclophosphamide.**
:08:53 Q. **If we turn to PDX-9-45, does the patent disclose the**

:09:00 **structure of cyclophosphamide?**

:09:02 A. **It does, indeed.**

:09:03 Q. **Is cyclophosphamide a nitrogen mustard?**

:09:07 A. **Yes, it is.**

:09:07 Q. **How do we know that?**

:09:08 A. **Because it has the nitrogen with the two arms and the chlorines attached.**

:09:13 Q. **And what expectation would a person of ordinary skill in the art have about the reaction mechanism for degradation by hydrolysis of cyclophosphamide?**

:09:23 A. **So, again, having the same functional group, it's likely to have the same reactivity and mechanism.**

:09:31 Q. **If you turn to Column 7, Lines 32 to 39 of DTX-349, the Alexander patent, what solvent does Alexander use in the pre-lyophilization solution for cyclophosphamide?**

:09:48 A. **Water.**

:09:48 Q. **If we could go to PDX-9-47, I want to turn to the third subject of your testimony, some references that discuss bendamustine in particular.**

:10:12 **If we go to JTX-55 in your binder, it's the Olthoff patent, have you heard some testimony about that, sir?**

:10:20 A. **I have, indeed.**

:10:34 **MR. WIESEN: This is another German reference, Your Honor, that has a translation.**

BY MR. WIESEN:

Q. Turn to Page 905. If we call up Slide PDX-9-49.

What type of solvents does Olthoff talk about?

A. So he talked about monovalent alcohols, that's molecules with one of those OH groups on them, glycols that have two, and polyvalent alcohols, so many.

Q. And is TBA a monovalent alcohol, a polyvalent alcohol, or a glycol?

A. TBA is a monovalent alcohol.

Q. How many compounds would be monovalent alcohols?

A. Scores.

Q. How many compounds would be monovalent alcohols, glycols, or other polyvalent alcohols?

A. I dread to count. Lots.

Q. Does Olthoff provide any example of bendamustine with TBA?

A. No.

Q. If you turn to Page 907 in the translation, we have it on the slide, PDX-9-50, what particular solvents does Olthoff exemplify with bendamustine?

A. So he exemplifies with three. So ethanol abs. refers to something that is called absolute ethanol. It's the highest grade of anhydrous ethanol that one can typically buy. So it's anhydrous ethanol, propylene glycol, and glycerol.

:12:16 Q. **Are these the only three specific examples of solvents**
:12:20 **Olthoff uses with bendamustine?**
:12:24 A. **Yes, they are the only three.**
:12:27 Q. **Just to be clear, Dr. Welton, is Olthoff actually**
:12:34 **discussing here a pre-lyophilization solution?**
:12:38 A. **Well, Olthoff is recommending that you don't**
:12:41 **lyophilize at all.**
:12:42 Q. **Does it matter for the solvent effects what the**
:12:45 **solution is going to be used for?**
:12:47 A. **No, no. The solvent effects are entirely independent**
:12:50 **of what happens at whatever point it is that your solution**
:12:54 **is arriving to. It makes no difference.**
:12:57 Q. **I want to turn, then, to DTX-332 in your binder. If**
:13:05 **we could have PDX-9-52. I am not sure we have heard much**
:13:15 **about this paper and we will be brief with it.**
:13:18 **Are you familiar with the Scasnar reference?**
:13:21 A. **I am, indeed.**
:13:21 Q. **You see in the title, it refers to 14C Cytostasan?**
:13:28 A. **Yes.**
:13:28 Q. **Do you have an understanding of what that is?**
:13:30 A. **Yes. So Cytostasan is yet another name for**
:13:34 **bendamustine. The 14C tells you that it's been radiolabeled**
:13:41 **with carbon 14 so that you can do the tracking experiments**
:13:46 **they discuss in this paper.**
:13:47 Q. **And if you turn briefly to PDX-9-53. It's Table 1**

from the Scasnar paper. What does this disclose?

MR. DAIGNAULT: Objection, Your Honor. This is not in his expert report.

THE COURT: Okay.

MR. DAIGNAULT: There is one paragraph.

MR. WIESEN: Can we chat off the record?

THE COURT: Yes.

(Pause.)

MR. WIESEN: Your Honor, I guess another dispute on this one.

THE COURT: All right, counsel. Let's talk.

(The following took place at sidebar.)

MR. DAIGNAULT: Your Honor, our position is this chart, this discussion, is not disclosed in this report. This cite is the cover page of Scasnar. He is just not talking about, highlighting this table and it's not part of -- one-paragraph discussion in Paragraph 43.

MR. WIESEN: Your Honor, our view is that the discussion here -- he is right. The cite is to the paper generally. It discusses the various aqueous infusion media. And those are what's contained in the table, and that's pretty much the only point we are going to bring out, that these are the media that are discussed with bendamustine.

MR. DAIGNAULT: But it goes beyond that.

THE COURT: In what way?

MR. DAIGNAULT: Because I believe he is going to somehow use that table to support his opinion which he hasn't testified to.

THE COURT: Do you want to wait and see if Mr. Wiesen attempts to elicit that?

MR. DAIGNAULT: I can do that.

MR. WIESEN: I will limit it.

THE COURT: Thank you.

(End of sidebar conference.)

THE COURT: I will overrule the objection at this point as a result of our discussion at sidebar.

MR. WIESEN: Thank you.

BY MR. WIESEN:

Q. **Dr. Welton, going back to Table 1 in Scasnar, how many different solvents with bendamustine are discussed in this table?**

MR. DAIGNAULT: Objection, Your Honor.

THE COURT: How many different?

MR. WIESEN: That was the question, Your Honor.

THE COURT: You are objecting to that?

MR. DAIGNAULT: It's not in his expert report. I will withdraw it.

THE COURT: How many different?

You can answer the question.

THE WITNESS: One, two, three, four, five,

benzene twice, so, six, seven, eight.
BY MR. WIESEN:
Q. And is TBA one of them?
A. No.
Q. You can take that down, please.
Dr. Welton, we are almost done.
A. Thank you.
Q. If we could turn, then, to the patents. I want to look at the claims first of the '190 patent. If we could have PDX-9-60.
Claim 5 and 8, the asserted claims of the '190 patent, what is your understanding of what is claimed in Claim 5 of the '190 patent?
A. So this is the composition of the pre-lyophilization solution, and it's got the bendamustine in it.
Q. If we focus on the last element, if we could highlight that, of Claim 5, "Said tertiary-butyl alcohol is present in said pharmaceutical composition at a concentration of about ten to 50 percent volume over volume."
Do you see that?
A. I do see that.
Q. Do you have an opinion about whether, based on the prior art as a whole, a person of ordinary skill in the art would think it was obvious to use tertiary-butyl alcohol present at about ten to 50 percent in a pre-lyophilization

:19:00 **solution for bendamustine hydrochloride?**

:19:01 A. **No, it wouldn't be obvious.**

:19:03 Q. **Why not?**

:19:04 A. **So the literature gives you neither sufficient**

:19:10 **information to know that TBA would be successful nor a**

:19:18 **sufficient predictive capacity as to any amount that might**

:19:23 **be the appropriate amount to use.**

:19:24 Q. **And do you see Claim 8 technically depends from Claim**

:19:28 **5?**

:19:28 A. **Yes.**

:19:28 Q. **Do you have an opinion that's different for Claim 8 or**

:19:31 **is it the same analysis?**

:19:32 A. **No. Same analysis.**

:19:33 Q. **If we turn, then, to the '863 patent, asserted Claim**

:19:38 **1, PDX-9-61, do you see that it includes an element of a**

:19:44 **trace amount of tertiary-butyl alcohol?**

:19:47 A. **I see that it says that, yes.**

:19:48 Q. **What do you understand to be the source of the trace**

:19:51 **amount of the tertiary-butyl alcohol in Claim 1 of the '863**

:19:57 **patent?**

:19:57 A. **So it would have to be in the pre-lyophilization**

:19:59 **solution somewhere in order to turn up here.**

:20:02 Q. **Do you have an opinion whether it would have been**

:20:04 **obvious to a person of ordinary skill in the art to use**

:20:07 **tertiary-butyl alcohol in the pre-lyophilization solution**

for bendamustine hydrochloride?

A. So it would not have been obvious to use TBA.

Q. Why not?

A. Because the literature gives -- doesn't give you sufficient predictive capacity.

Q. And if we turn, finally, to the asserted claims of the '270, they are recited here on PDX-9-62. In your opinion, sir, would the prior art as a whole motivate a person of ordinary skill in the art and teach a person of ordinary skill in the art how to come up with a pre-lyophilization solution that will result in a lyophilized composition with the claimed stability?

A. No, it doesn't.

Q. Why not?

A. So there is nothing in the literature that is sufficiently precise to be able to say, if you do A the outcome will be X. And that's what it would require, if you could do that.

MR. WIESEN: May I have a moment, Your Honor?

THE COURT: Yes.

(Pause.)

MR. WIESEN: No further questions, Your Honor.

THE COURT: Let's take an early lunch for an hour, and have cross after lunch.

(Luncheon recess taken.)

Afternoon session, 1:12 p.m.

THE COURT: Good afternoon. Please take your seats.

Mr. Daignault, cross-examination.

MR. DAIGNAULT: Thank you very much, your Honor.

THE COURT: You're welcome.

MR. DAIGNAULT: May I approach the witness, your Honor?

THE COURT: Yes, sir.

(Binders handed to the Court.)

CROSS-EXAMINATION

BY MR. DAIGNAULT:

Q. **Good afternoon, Dr. Welton.**

A. **Good afternoon.**

Q. **I've handed you binders, exhibits, and also your deposition transcript, and I will refer to exhibits as we proceed.**

A. **Okay.**

Q. **So you went through your educational and professional background.**

When you were at the University of Sussex, during the course of your studies, you never were involved in the characterization of finished pharmaceutical dosage forms; is that right?

A. **No, I wasn't.**

:28:20 Q. **And so as far as your career is concerned, Dr. Welton,**
:28:27 **would it be fair to say that your area of focus is in**
:28:31 **various aspects of chemistry?**
:28:33 A. **Yes.**
:28:34 Q. **And so during the course of your entire career, have**
:28:39 **you ever done work in characterizing finished pharmaceutical**
:28:44 **dosage forms?**
:28:44 A. **No, not at all.**
:28:46 Q. **And during the course of your career, you never were**
:28:51 **involved in developing a finished pharmaceutical dosage**
:28:55 **form; is that right?**
:28:55 A. **That's correct.**
:28:56 Q. **And in your CV you list various papers; is that**
:29:03 **right?**
:29:03 A. **I do.**
:29:03 Q. **And none of the papers that you list in your CV**
:29:09 **relate to finished pharmaceutical dosage forms; isn't that**
:29:11 **correct?**
:29:12 A. **That's correct.**
:29:12 Q. **And you also list editorials, books and book chapters**
:29:17 **and some patents and published conference proceedings and**
:29:20 **other publications; is that right?**
:29:22 A. **Yes.**
:29:22 Q. **And none of those areas, none of those things involved**
:29:25 **work relating to finished pharmaceutical dosage forms; isn't**

:29:28 **that right?**

:29:29 A. **That's correct.**

:29:29 Q. **And have you ever been involved in characterizing or developing a lyophilized composition that would then be reconstituted and diluted for injection into a patient?**

:29:44 A. **No, never.**

:29:45 Q. **And have you ever used tertiary butyl alcohol as a solvent in any of the lyophilization projects that you've undertaken during your career?**

:29:54 A. **I don't believe so.**

:29:57 Q. **And you never have used ethanol as a pre-lyophilization solution solvent; isn't that right?**

:30:04 A. **Again, I don't believe so.**

:30:06 Q. **And you have never used any monovalent alcohols as a solvent in a pre-lyophilization process; isn't that right?**

:30:13 A. **Not as the main solvent, no.**

:30:15 Q. **And those pre-lyophilized solutions that you prepared, you never included what I will call a bulking agent; isn't that right?**

:30:24 A. **No, never.**

:30:38 **MR. DAIGNAULT: Sorry. I forgot one binder. If I may, your Honor?**

:30:40 **THE COURT: You my you may.**

:30:45 **(Mr. Daignault handed a binder to the witness**
:30:47 **and the Court.)**
:30:50 **BY MR. DAIGNAULT:**
:31:12 Q. **Now, Dr. Welton, do you recognize this to be a copy of**
:31:15 **your expert report in this case?**
:31:16 A. **Yes, I do.**
:31:17 Q. **And could you please turn to paragraph 23 of your**
:31:25 **expert report?**
:31:28 **MR. WIESEN: Your Honor, I don't know if he**
:31:30 **needs to impeach him or what the purpose is. Perhaps he**
:31:34 **could ask a question first and see if the report is**
:31:36 **necessary.**
:31:36 **THE COURT: What are you referring to?**
:31:37 **MR. DAIGNAULT: I just want to ask a statement**
:31:39 **in Dr. Welton's expert report that he made.**
:31:41 **THE COURT: You can ask him about his views,**
:31:43 **his opinions. If they conflict with what he said in his**
:31:46 **expert report, you can use the expert report as a prior**
:31:50 **statement.**
:31:50 **MR. DAIGNAULT: Yes. I just thought it would be**
:31:52 **easier.**
:31:52 **THE COURT: It doesn't comply with the Rules of**
:31:54 **Evidence. It may be easier.**
:31:56 **MR. DAIGNAULT: Right. You're right, your**
:31:58 **Honor.**

:31:58 **THE COURT: Okay.**

:31:58 **BY MR. DAIGNAULT:**

:31:59 Q. **Dr. Welton, let's put that book aside.**

:32:07 **Now, Dr. Welton, would you agree with this**

:32:11 **statement: "Nitrogen mustards are highly reactive chemical**

:32:14 **compounds that react with various nucleophiles such as DNA**

:32:19 **bases via electrophilic aziridinium intermediate"?**

:32:25 A. **Yes.**

:32:25 Q. **And I believe you cited a 1976 paper, the Williamson**

:32:29 **paper; is that right?**

:32:30 A. **I have to check which one I cited to.**

:32:34 **THE COURT: It's not a memory test.**

:32:45 **THE WITNESS: All right.**

:32:46 **THE COURT: Mr. Daignault, what paragraph did**

:32:48 **you read that from?**

:32:49 **MR. DAIGNAULT: That was paragraph 23, your**

:32:50 **Honor.**

:32:50 **(Pause.)**

:32:59 **MR. DAIGNAULT: Sorry. I wasn't sure if I heard**

:33:01 **an answer to the question.**

:33:02 **THE COURT: He's looking.**

:33:03 **THE WITNESS: I found it. I found it.**

:33:04 **BY MR. DAIGNAULT:**

:33:05 Q. **Would you agree with that statement?**

:33:06 A. **Well, say it again.**

:33:08 Q. **It's the third sentence. "Nitrogen mustards are highly reactive chemical compounds that react with various nucleophiles such as DNA bases via electrophilic aziridinium intermediate."**

:33:24 **You cite the Williamson 1967 paper?**

:33:27 A. **Yes.**

:33:28 Q. **And at the top do you also agree with this statement, Dr. Welton? "Bendamustine belongs to the nitrogen mustard family of alkylating agents which attack cancer cells by chemically binding to their DNA in an alkylation reaction"?**

:33:48 A. **Yes, I do.**

:33:49 Q. **Would you also agree with this statement, Dr. Welton: "One of the most" -- sorry. I'll start again.**

:34:13 **"Although nitrogen mustard compounds like bendamustine are designed to bind with DNA bases, their considerable reactivity means they can occasionally react with other neutrophiles as well as under the proper circumstances"?**

:34:26 A. **Yes, that's correct.**

:34:28 Q. **And one of the most common other nucleophiles that mustard compounds regularly react with is water; is that correct?**

:34:39 A. **That's correct.**

:34:40 Q. **Is that right?**
:34:41 A. **Yes.**
:34:41 Q. **Which is a major solvent present in both intravenous**
:34:45 **infusion and the body itself?**
:34:46 A. **Yes, absolutely.**
:34:48 Q. **And so, Dr. Welton, you focused on the dissimilarities**
:35:02 **between certain chemical compounds that you discussed during**
:35:05 **your direct examination; is that right?**
:35:07 A. **Yes, I did in one part, yes.**
:35:10 Q. **And isn't it correct that every chemical compound is**
:35:13 **not the same?**
:35:14 A. **That's correct.**
:35:17 Q. **Right. Every chemical compound is dissimilar; isn't**
:35:22 **that right?**
:35:22 A. **No. The same and dissimilar aren't the same thing.**
:35:28 **Dissimilar means substantially or different whereas**
:35:34 **substantially different -- whereas not the same just means**
:35:37 **not the same. They can be similar and not be the same.**
:35:41 Q. **Well, each chemical compound has its own unique**
:35:44 **chemical structure; isn't that right?**
:35:46 A. **That's correct, yes.**
:35:47 Q. **But there are also similarities between chemical**
:35:49 **compounds; isn't that right?**
:35:50 A. **Yes, that's correct, too.**
:35:52 Q. **And so let's focus on the similarities of chemical**

:35:56 **compounds.**

:35:57 **In this case, we're talking about, one of the**

:36:01 **issues we discussed can discussed is hydrolysis?**

:36:04 A. **Yes, we discussed hydrolysis.**

:36:07 Q. **And a chemical compound that hydrolyzes has a**

:36:11 **constituent part on the molecule that reacts with water;**

:36:16 **isn't that right?**

:36:16 A. **Yes, that's correct.**

:36:17 Q. **And if a chemical compound reacts with oxygen, there's**

:36:21 **an oxygen on that molecule; isn't that right? An oxidation**

:36:26 **reaction?**

:36:27 A. **If a chemical compound reacts with oxygen, there does**

:36:30 **not have to be an oxygen on the molecule in the first place.**

:36:34 **After the reaction, there will be, there will be an oxygen**

:36:37 **on the molecule.**

:36:38 Q. **Right. The oxygen is reacting with the constituent**

:36:42 **part on the molecule causing an oxidation reaction; is that**

:36:46 **right?**

:36:46 A. **That would be an oxidation reaction.**

:36:47 Q. **And so there are hydrolysis --**

:36:49 A. **I should say there are other kinds of oxidation**

:36:52 **reactions that actually don't involve oxygen transfer at**

:36:56 **all.**

:36:56 Q. **But there are hydrolysis prone compounds and compounds**

:36:59 **that are not prone to hydrolysis; isn't that right?**

:37:01 A. **So you have to be careful with that because there are**
:37:07 **compounds that will react with water, and so I don't know**
:37:14 **whether you're talking about the -- ultimately, the**
:37:18 **compounds, that long enough it would react with water or**
:37:22 **whether you will say that the compound would react with**
:37:25 **water quickly. So could you please make a distinction.**
:37:29 Q. **I'm just talking about chemical compounds, chemical**
:37:32 **compounds that react with water, that's a hydrolysis**
:37:35 **reaction; isn't that right?**
:37:36 A. **Chemical compounds -- there's also a reaction called a**
:37:40 **hydration reaction, which is not the same as a hydrolysis**
:37:44 **reaction.**
:37:45 Q. **But a hydrolysis reaction is a reaction in water;**
:37:49 **isn't that right?**
:37:49 A. **A hydrolysis reaction is a reaction with water,**
:37:52 **yes.**
:37:53 Q. **Chemical compounds that have, that react in that**
:37:57 **manner, that hydrolyze, they're reacting with water; isn't**
:38:00 **that right?**
:38:00 A. **Chemical compounds that hydrolyze are reacting with**
:38:04 **water, yes.**
:38:05 Q. **And as a nitrogen mustard, a person of ordinary skill**
:38:08 **in the art for 2005 would have reasonably expected**
:38:12 **bendamustine to be a highly reactive chemical compound that**
:38:17 **can react with water; isn't that right?**

:38:21 A. **Well, they wouldn't need to expect. It would have**
:38:25 **already been demonstrated in the literature they could react**
:38:28 **with water.**
:38:28 Q. **Right. Okay. Yes. In fact, before 1995, sorry,**
:38:33 **2005, that was known?**
:38:34 A. **Yes.**
:38:35 Q. **And it was known also that the reaction produced HP1**
:38:43 **and HP2; isn't that right?**
:38:45 A. **Yes. That was known.**
:38:47 Q. **Now, Dr. Welton, isn't one of the most straightforward**
:39:14 **ways of getting around hydrolysis is to not use water?**
:39:19 A. **Yes, absolutely.**
:39:21 Q. **And another approach to the problem of hydrolysis is**
:39:29 **to reduce the amount of water; isn't that correct?**
:39:33 A. **One wouldn't expect it to be as effective, but it is**
:39:39 **an available alternative, yes.**
:39:42 Q. **It is an available alternative; isn't that right?**
:39:45 A. **Yes, it is an available alternative.**
:39:46 Q. **So, for example, a person of ordinary skill in the art**
:39:49 **could introduce a non-aqueous solvent with water to reduce**
:39:55 **hydrolysis; isn't that right?**
:39:56 A. **So it is one of the available alternatives, but you**
:40:02 **have no way of knowing that, one, it will be effective, or,**
:40:08 **two, how effective it will be until you do it.**
:40:16 Q. **But that is something you could observe by adding a**

:40:21 **co-solvent in certain concentrations to water; isn't that**
:40:25 **right?**
:40:25 A. **That is something that you could do experiments to**
:40:31 **observe, yes.**
:40:32 Q. **All right. I'd like to show you some testimony from**
:40:35 **Mr. Brittain at trial.**
:40:36 A. **Okay. Where is that?**
:40:39 Q. **It will be on the screen. I actually have a**
:40:42 **printout as a demonstrative if you would like it. This is**
:40:45 **DDX-1.**
:40:49 A. **Oh.**
:40:50 Q. **Would you like a paper copy?**
:40:51 A. **No, no. I can see it.**
:40:53 Q. **Now, you were here for Mr. Brittain's trial testimony;**
:40:57 **is that right?**
:40:57 A. **I was here. I must confess, I wasn't listening**
:41:01 **terribly closely.**
:41:03 Q. **And the question to Mr. Brittain:**
:41:13 **"And, Mr. Brittain, when a chemist is trying to**
:41:16 **predict the effect of a solvent, it's important that the**
:41:19 **chemist understand the chemical reaction, the chemical**
:41:24 **mechanism by which the reaction occurs; isn't that right?"**
:41:27 **And he says "yes"?**
:41:28 A. **Yes.**
:41:28 Q. **"And so if the drug is oxygen sensitive, you add an**

:41:31 **antioxidant; right"?**

:41:33 **He says "yes."**

:41:34 **"And so if the drug is sensitive to light, you put it in an enclosed dark container; right?**

:41:40 **"Yes.**

:41:41 **"And so if the chemical reaction is one that involves hydrolysis, then you try to remove the water; isn't that correct?**

:41:47 **"Yes.**

:41:48 **"So I believe what we were talking about, Mr. Brittain, you just mentioned that if you have a hydrolysis problem, then you either remove the water or use less water?**

:41:58 **"That's correct.**

:42:00 **"And so by using increased amounts of TBA, you are using less water in the pre-lyophilization solution; isn't that right?**

:42:07 **"Yes."**

:42:08 **Do you agree with Mr. Brittain's testimony?**

:42:09 A. **I believe that using TBA is one of the available alternatives to try and reduce the, the level of hydrolysis. It is in no way the only one. In other words, there are -- you know, if you absolutely want a guarantee to stop the hydrolysis, you have to not have water present, and then once you find that you have failure for some reason that**

:42:13
:42:15
:42:22
:42:24
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:42:31

you're anhydrous and you chose to do it by this kind of, adding the water back in, then it's, it's something that one might try, yes.

Q. Right. And as a person of ordinary skill in the art is adding co-solvent with water in various concentrations, he or she could determine the resulting level of degradation; isn't that right?

A. Yes, you could do it to determine that, yes.

Q. And were you here for Dr. Kamat's testimony?

A. I was.

MR. DAIGNAULT: Can we please have that? I'm sorry. Just for the record, the Brittain trial transcript, testimony is at the transcript December 1st, Page 219 at lines 24 to Page 220, line 14, Page 227, lines 7 through 14.

BY MR. DAIGNAULT:

Q. Now let's take a look at Dr. Kamat's testimony, please.

Dr. Kamat said, the main advantages of lyophilization is really the stability, and the aqueous stability. As we know, forming some compounds are very vulnerable to hydrolysis. They are created by hydrolysis. How do you stop it? We either freeze them to minus 70 or 80 degrees or just freeze dry them and keep them at room temperatures.

THE COURT: Yes?

:44:02 **MR. WIESEN: I'm going to object to this**
:44:04 **testimony. It's beyond the scope of Dr. Welton's direct.**
:44:07 **We specifically limited him to the pre-lyophilization**
:44:09 **solution, and this is about the stability of the lyophilized**
:44:13 **product.**
:44:13 **MR. DAIGNAULT: This goes directly to the**
:44:15 **pre-lyophilized solution. We're talking about the**
:44:17 **pre-lyophilization solution being frozen at this**
:44:21 **temperature, so he's talking about the stability of the**
:44:23 **pre-lyophilization solution in the lyophilization process.**
:44:03 **MR. WIESEN: If he is going to ask about the**
:44:05 **pre-lyophilization solution, I will withdraw the objection.**
:44:07 **THE COURT: All right.**
:44:09 **BY MR. DAIGNAULT:**
:44:10 Q. **"So we have removed the water. Once we remove the**
:44:13 **water, all the reactions stop, hydrolysis stops. That is a**
:44:18 **key. We remove the water."**
:44:20 **Do you see that testimony?**
:44:21 A. **I do see that testimony, yes.**
:44:22 Q. **And again, if you remove or reduce the amount of water**
:44:27 **in a co-solvent system, then that will either reduce or**
:44:31 **eliminate hydrolysis, depending on how much of the**
:44:35 **nonaqueous co-solvent is added to water. Isn't that right?**
:44:39 A. **So I do need to check what you are talking about.**
:44:43 **When we freeze them, we are in the lyophilizer,**

:44:47 **I said very clearly I was talking about what happens before**
:44:50 **you get to the lyophilizer. The freezing happens in the**
:44:52 **lyophilizer.**
:44:53 Q. **I understand.**
:44:54 A. **So in the liquid pre-lyophilization solution, you are**
:45:00 **asking me what?**
:45:02 Q. **Again, in the pre-lyophilization solution, if you use**
:45:06 **a nonaqueous co-solvent with water, you can reduce or**
:45:10 **eliminate hydrolysis, depending on the concentration of that**
:45:15 **co-solvent that is added. Isn't that right?**
:45:17 A. **As I made clear, if you have water present, in fact,**
:45:21 **if you have water present, you can't eliminate. You might**
:45:24 **slow the reaction down, but you are not going to stop it.**
:45:27 **It will happen with time. So eliminate would be no.**
:45:30 Q. **Because of ambient water, you are talking about?**
:45:32 A. **No, eliminate would be no, because if it's got water**
:45:35 **in the mixture, then it will react with that water, you**
:45:40 **know, at the rate that it reacts with that water.**
:45:43 **Eliminate means stop entirely. The answer to**
:45:47 **the word eliminate is no. The answer to your question about**
:45:51 **reduce, it would be one of the available alternatives that**
:45:54 **one might try.**
:45:55 Q. **What about Dr. Kwan's testimony, again, "In this**
:46:07 **particular case, yes, because the POSA would know**
:46:10 **bendamustine hydrochloride is unstable in water, and once he**

:46:13 **confirms that with his own screening experiment, which is**
:46:16 **part of the routine start, for any process, then the next**
:46:19 **step could be to consider evaluating co-solvent system,**
:46:23 **thereby reducing the amount of water and less exposure of**
:46:26 **bendamustine and less degradation."**
:46:29 **You would agree with that statement?**
:46:31 A. **If one's first attempt failed, one is forced to then**
:46:36 **move to other options after the failure of the first**
:46:42 **attempt, which would be the result of a series of**
:46:46 **experiments.**
:46:46 Q. **One of the first attempts a person of ordinary skill**
:46:49 **in the art might do is to conduct some stability studies to**
:46:53 **look at the profile of the compound in water alone. Right?**
:46:57 A. **Yes.**
:46:57 Q. **Because water is the preferred solvent. Isn't that**
:47:03 **right? Water is the preferred pre-lyophilization solvent.**
:47:07 **Isn't that right?**
:47:07 A. **It's the most common. Yes.**
:47:09 Q. **But if the water alone as a pre-lyophilization solvent**
:47:12 **was not acceptable, then one of the options would be to use**
:47:15 **a nonaqueous co-solvent with water. Isn't that right?**
:47:21 A. **That's one of the available alternatives, yes.**
:47:23 Q. **So, Dr. Welton, a person of ordinary skill in the art**
:47:37 **in 2005 would have the skills and knowledge to evaluate**
:47:40 **solubility of material in a solvent. Isn't that correct?**

:47:45 A. **Yes, they would.**

:47:46 Q. **And it would be correct, Dr. Welton, to say that a person of ordinary skill in the art in 2005 had the skills and knowledge to evaluate the solubility of bendamustine in solvents. Isn't that right?**

:47:54

:47:58

:48:01

:48:03 A. **Yes, that's correct.**

:48:05 Q. **And these solubility studies that we are talking about, this is something that would have been taught to undergraduate chemistry students. Isn't that right?**

:48:36

:48:38

:48:42 A. **Oh, yes, absolutely.**

:48:43 Q. **Also, Dr. Welton, isn't it correct that in 2005 a pharmaceutical formulator would be familiar with factors such as chemical reactivity, solubility, physical properties and compatible with excipients in choosing a formulation technique?**

:49:04

:49:07

:49:13

:49:18

:49:19 A. **Yes, they would be.**

:49:20 Q. **And isn't it correct, Dr. Welton, that persons of ordinary skill in the art bring their knowledge and experience and creativity to bear when they are conducting pharmaceutical development work?**

:49:24

:49:27

:49:31

:49:32 A. **Yes, they do.**

:49:33 Q. **And a person of ordinary skill in the art would also consult the literature in his or her work in developing a formulation product. Isn't that right?**

:49:38

:49:42

:49:43 A. **Yes, they do.**

:49:44 Q. **And so a person of ordinary skill in the art, according to Cephalon's definition, would have had at least five or three years of experience formulating, characterizing and analyzing pharmaceutical products. Isn't that correct?**

:50:02 A. **That's correct.**

:50:02 Q. **So when we talk about issues like chemical reactivity, solubility, physical properties, capability with excipients, again, a person of ordinary skill in the art would bring his or her years of experience in looking at those kinds of factors. Isn't that correct?**

:50:23 A. **Yes, they would.**

:50:24 Q. **And they would have had experience in addressing those factors, not just knowing that those factors exist but a pharmaceutical formulator with those years of experience would know the ways in which to address those issues. Isn't that right?**

:50:49 A. **So it would depend on which of those issues had cropped up in their career previously. But there is no reason to suspect not.**

:50:56 Q. **And the end goal for a pharmaceutical formulator is to develop an acceptable pharmaceutical dosage form. Right?**

:51:16 A. **Yes.**

:51:17 Q. **Dr. Welton, I would like you to please turn to what is DTX-343, the Olthoff 1983 paper.**

:51:40 A. **DTX?**

:51:41 Q. **343.**

:51:43 A. **Thank you, yes.**

:51:44 Q. **I believe there is the English translation on the back?**

:51:51 A. **Yes, I have found it.**

:51:52 Q. **If I could draw your attention to what is DTX-343 at 0011, it's at Page 11.**

:52:03 A. **Yes, I have got that.**

:52:06 Q. **Do you see the statement in the second paragraph beginning with "Bendamustine hydrochloride is"?**

:52:07 **Sorry, first paragraph. It begins, "Bendamustine hydrochloride is."**

:52:18 A. **Yes.**

:52:20 Q. **That is the chemical structure of bendamustine hydrochloride?**

:52:27 A. **Yes, it is.**

:52:27 Q. **And it says, "In 1971, the compound was introduced as pharmaceutical preparation under the trade name Cytostasan."**

:52:36 **Do you see that?**

:52:36 A. **I do, yes.**

:52:37 Q. **And when it says .025 grams, what is that in milligrams?**

:52:42 A. **Sorry?**

:52:48 Q. **When it says .025 grams, what is that in milligrams?**

:52:48

:52:49

:52:55

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:53:03 A. **That's 25 milligrams.**

:53:07 Q. **And if you look at the second paragraph, the first sentence, "Bendamustine hydrochloride is a relatively instable compound. Its mustard halogen groups are almost completely hydrolyzed in aqueous solutions after a short period of time."**

:53:33 **Do you see that?**

:53:34 A. **That's what it says, yes.**

:53:35 Q. **That would have been known to a person of ordinary skill in the art before 2005. Isn't that right?**

:53:41 A. **Yes. It's here.**

:53:44 Q. **And then it talks about some kinetic experiments. The next sentence, that one right there, can you please read that statement?**

:53:59 A. **"The kinetic experiments regarding the chloride hydrolysis of the N-mustard group of the bendamustine hydrochloride showed a reaction course in acid and neutral solutions which could be calculated according to the pseudo-first order of the reaction for a consecutive reaction of the symmetric di-halogen compound."**

:54:18 Q. **So that would have been known to a person of ordinary skill in the art in January 2005. Right?**

:54:25 A. **Yes.**

:54:25 Q. **Now, Olthoff talks about preparing a liquid formulation of bendamustine. Right?**

:54:31

:54:34 A. That's what he prefers, yes.
:54:36 Q. He also talks about lyophilized compositions. Right?
:54:41 A. He does, yes.
:54:42 Q. If we can turn to Page 0013 of DTX-343, if we could
:54:53 look at that paragraph that begins "The disadvantage."
:55:01 A. Yes.
:55:02 Q. Can you read that sentence, please?
:55:05 A. "The disadvantage of the extreme hygroscopicity of the
:55:11 lyophilisate," which is the post-lyophilization compound.
:55:11 Q. That's the key. Right?
:55:11 A. Yes. The hygroscopicity, I should point out, is not
:55:11 the same thing as being hydrolytically unstable.
:55:11 Q. Oh, I know.
:55:12 A. "...can be eliminated by the addition of polyols which
:55:16 are solid at room temperature, such as in particular
:55:20 mannitol."
:55:20 Q. So a person of ordinary skill in the art would have
:55:42 known that there were hygroscopicity issues with
:55:45 bendamustine in a lyophilized cake. Right?
:55:50 A. Yes.
:55:50 Q. And those issues, those concerns could be eliminated
:55:53 by using mannitol. Right?
:55:54 A. That's what it says, yes.
:55:55 Q. And if we could turn now to the paragraph below, the
:56:00 last paragraph, beginning "Surprisingly." The first

:56:10 **sentence, "Surprisingly," I believe you referred to this**
:56:14 **sentence in your direct examination. Is that right?**
:56:17 A. **Oh, yes.**
:56:17 Q. **And you said there are scores of monovalent alcohols.**
:56:20 **Is that right?**
:56:21 A. **There are.**
:56:21 Q. **Again, you have never worked with any monovalent**
:56:25 **alcohols to prepare a pre-lyophilization solution. Isn't**
:56:28 **that right?**
:56:29 A. **That's correct, yes.**
:56:29 Q. **And TBA is a monovalent alcohol. Right?**
:56:32 A. **It is, indeed.**
:56:33 Q. **And so is ethanol?**
:56:34 A. **It is, indeed.**
:56:35 Q. **Do you know how many of the solvents that you**
:56:37 **addressed in your direct examination were monovalent**
:56:40 **alcohols?**
:56:42 A. **Specifically?**
:56:44 Q. **If you recall.**
:56:48 A. **Ethanol and TBA I remember talking about.**
:56:55 **There was one in the chart where you asked me to**
:56:59 **count but not say the names.**
:57:20 Q. **Until Olthoff, Olthoff discloses a liquid formulation**
:57:25 **of bendamustine. Right?**
:57:28 A. **That's what he prefers, yes, sir.**

:57:29 Q. **As we discussed, it also talks about a lyophilized composition. Right?**

:57:35 A. **There are comments about lyophilized compositions, yes.**

:57:36 Q. **And Olthoff was published in 1983. Isn't that correct?**

:57:41 A. **That's correct.**

:57:41 Q. **And we know that later, in the 1990s, Ribomustin was sold in Europe as a lyophilized composition. Isn't that right?**

:57:50 A. **Yes, it was.**

:57:51 Q. **Ribomustin was not a liquid formulation. Right?**

:57:54 A. **No, it wasn't. Yes, you are right. No, it wasn't.**

:57:59 Q. **Let's talk a little bit about these stability studies. A person of ordinary skill in the art trying to determine what a stabilizing concentration of an organic solvent for -- I will stop there. That person of ordinary skill in the art would conduct stability studies using various concentrations of, let's assume there is a co-solvent in water, so at various concentrations of a nonaqueous co-solvent. Isn't that right?**

:58:51 A. **That's where you would start, yes.**

:58:52 Q. **Through those studies of various concentrations of the nonaqueous co-solvent in water, the person of ordinary skill in the art could then determine what is the stabilizing**

:59:04 **concentration for an acceptable pre-lyophilization solution.**
:59:08 **Isn't that right?**
:59:09 A. **So if it turned out that there was a concentration --**
:59:16 **well, it wouldn't turn out that there was a concentration at**
:59:19 **which there was no hydrolysis. If it turned out that there**
:59:22 **was a concentration at which you knew there was a certain**
:59:25 **amount of hydrolysis, it wouldn't be sufficient because we**
:59:31 **haven't yet considered the temperature variable because, of**
:59:34 **course, the hydrolysis would also be sensitive to the**
:59:37 **temperature at which the reaction was occurring.**
:59:39 Q. **Right. And in this particular situation, a person of**
:59:43 **ordinary skill in the art would generally understand that a**
:59:47 **pharmaceutical pre-lyophilization solution may be kept at**
:59:50 **ambient temperature for a certain amount of time. Isn't**
:59:53 **that right?**
:59:53 A. **It might, yes.**
:59:54 Q. **And a person of ordinary skill in the art would**
:59:57 **understand that a pre-lyophilization solution would be**
:59:59 **placed in a lyophilizer at a certain temperature. Isn't**
:00:03 **that right?**
:00:05 A. **So they wouldn't know in advance of knowing what**
:00:09 **temperature it was going to be in the lyophilizer what that**
:00:12 **temperature would be. And similarly, ambient is important.**
:00:15 **We don't know what the ambient temperature is, because**
:00:18 **unlike room temperature, which has a formal scientific**

:00:22 **definition, ambient temperature is the temperature at which**
:00:25 **one finds rooms.**
:00:26 **Of course, different rooms are at different**
:00:29 **temperatures. So, yes, it would be held to ambient**
:00:34 **temperature. But we don't know what ambient temperature is**
:00:36 **unless we know what we are talking about.**
:00:26 Q. **Right. But a person of ordinary skill in the art**
:01:03 **would take a look at different concentrations of co-solvent**
:01:07 **and might vary the temperature and run those kinds of**
:01:09 **studies; isn't that right?**
:01:11 A. **Yes. You could -- what you -- what you would do is**
:01:16 **you would, you would center a research protocol where you**
:01:22 **looked at the, the effect of temperature and the effect of**
:01:27 **concentration, which, of course, are correlated, and so**
:01:32 **you -- it gets quite complex. But that's what you do.**
:01:37 Q. **All right. And this is something that you teach to**
:01:38 **your students; is that right?**
:01:40 A. **Yes.**
:01:41 Q. **And getting back to Ribomustin for one moment, if**
:01:58 **a person of ordinary skill in the art were looking to**
:02:00 **develop a bendamustine hydrochloride composition, that**
:02:06 **person of ordinary skill in the art would try and learn as**
:02:08 **thoroughly as much as possible about Ribomustin; isn't that**
:02:12 **right?**
:02:12 A. **Yes.**

:02:14 Q. **And also, so in addition to the stability studies we**
:02:27 **talked about, a person of ordinary skill in the art would**
:02:29 **also study the reconstitution time of the composition that**
:02:33 **they were developing; isn't that right?**
:02:35 A. **Yes.**
:02:42 Q. **And the person of ordinary skill in the art would also**
:02:44 **consider the characteristics of the cake that is formed**
:02:47 **after the lyophilization process; isn't that right?**
:02:49 **MR. WIESEN: Objection, your Honor.**
:02:50 **THE COURT: Sustained.**
:02:52 **MR. WIESEN: This is beyond -- thank you.**
:02:54 **BY MR. DAIGNAULT:**
:03:04 Q. **Dr. Welton, let's take a look at the Ni reference is,**
:03:09 **which is JTX-079.**
:03:27 **And, Dr. Welton, if I could draw your attention**
:03:30 **to the abstract?**
:03:31 A. **Mm-hmm.**
:03:32 Q. **The sentence that begins: Neat tertiary butyl**
:03:37 **alcohol.**
:03:38 **Do you see that?**
:03:39 A. **I do.**
:03:43 Q. **So Ni is saying here, Neat tertiary butyl alcohol,**
:03:48 **TBA, and she's talking about TBA.**
:03:51 A. **Neat means anhydrous.**
:03:53 Q. **Right. Right. But then she mentions, a low toxicity,**

:03:57 **high vapor pressure, and low melting solvent.**

:04:00 **So those adjectives, she's talking about TBA;**

:04:04 **isn't that right?**

:04:05 A. **She is.**

:04:05 Q. **And there are advantages to using a co-solvent with**

:04:17 **low toxicity in formulating a pre-lyophilization solution;**

:04:22 **isn't that right?**

:04:23 A. **If it's a pre-lyophilization for pharmaceutical**

:04:28 **preparation, then, yes. Well, even actually generally,**

:04:33 **yes.**

:04:34 Q. **And also high vapor pressure. There's an advantage to**

:04:40 **using a co-solvent with high vapor pressure in a**

:04:46 **pre-lyophilization solution; isn't that correct?**

:04:48 A. **If you're going to go on and lyophilize, then,**

:04:52 **yes.**

:04:52 Q. **And there's also an advantage, Dr. Welton, of using a**

:04:58 **co-solvent like TBA that has a low melting point; isn't that**

:05:03 **right?**

:05:04 A. **So you wouldn't want the melting point to be too low,**

:05:15 **but, yes.**

:05:18 Q. **And so, again, Ni is saying that TBA has low toxicity,**

:05:31 **high vapor pressure and low melting; isn't that right?**

:05:33 A. **That is what she says, yes.**

:05:35 Q. **And if I draw your attention to page 40 of this**

:05:50 **reference, which is --**

:05:55 A. **Page 40?**
:05:56 Q. **Page 40. So it's JTX-079, and the Bates number is**
:06:01 **ending in ending in 352. In the upper left corner it**
:06:08 **begins, "generally."**
:06:08 A. **"Generally," yes.**
:06:11 Q. **And can you read those first two sentences, Dr.**
:06:22 **Welton?**
:06:22 A. **"Generally, a product is freeze-dried, if it is not**
:06:26 **stable in aqueous media. Although inherently expensive in**
:06:29 **terms of manufacturing costs, freeze-drying is often the**
:06:32 **processing method of choice for the production of an**
:06:35 **unstable parental product."**
:06:37 Q. **You would agree with that statement. Right, Dr.**
:06:42 **Welton?**
:06:46 A. **So I would agree with the, that sentence.**
:06:53 **I don't know why he's standing up.**
:06:54 **MR. WIESEN: Your Honor, I think we ventured**
:06:55 **beyond the scope again of the stability of the**
:06:57 **pre-lyophilization.**
:06:58 **THE COURT: I think we have, Mr. Daignault.**
:07:00 **Sustained.**
:07:00 **BY MR. DAIGNAULT:**
:07:13 Q. **How about, I think this may be in your domain.**
:07:16 **The next paragraph that begins, the ideal freeze-drying**
:07:20 **medium.**

:07:29 **Do you see that first sentence, Dr. Welton?**

:07:32 A. **I'm looking at it.**

:07:34 Q. **That's what Ni mentions in her abstract; isn't that right? She talks about, these are considerations for the solvent having a high vapor pressure, melting point above room temperature, a high viscosity, and a low toxicity?**

:07:54 A. **Yes, that's what she said.**

:07:57 Q. **And she mentions in her abstract that TBA has these attributes; isn't that right?**

:08:02 A. **Well, so you remember how I equivocated over the, the low melting point in the abstract. You said you wouldn't want it too low. So she now is introducing equivocation.**

:08:23 Q. **All right. But generally these propositions are well understood by a person of ordinary skill in the art; isn't that right?**

:08:27 A. **What she's saying to be understood, yes.**

:08:31 Q. **And if we could look at Table 1 further down that page, there's a comparison between a few solvents that -- there are four solvents there, one of them being water; right?**

:08:59 A. **One is water, yes.**

:09:00 Q. **And what is HAc?**

:09:01 A. **HAc is acetic acid.**

:09:04 Q. **We know TBA. What is DSMO?**

:09:08 A. **Dimethyl sulfoxide.**

:09:09 Q. **And Table 1 shows is that TBA has the highest viscosity as well as the highest vapor pressure, isn't that right, of the four solvents mentioned?**

:09:18 A. **Of the four solvents mentioned here, but it's not a particularly high viscosity liquid.**

:09:27 Q. **Now, if we could turn to Page 44 of Ni, do you see the sentence in the upper left corner that begins, "Solvents with high viscosity"?**

:10:02 A. **"Solvents with high viscosity." I can't find it.**

:10:05 **MR. DAIGNAULT: Sorry. It's the next, the lower sentence, Mr. Vaughn, that begins, "Solvents with a high viscosity are likely."**

:10:12 **BY MR. DAIGNAULT:**

:10:15 Q. **Can you read that sentence, Dr. Welton?**

:10:18 A. **I can read that sentence, but I shan't just yet.**

:10:24 **MR. WIESEN: Objection, your Honor. It's not talking about the stability here. It's talking about other attributes of the case, so it's beyond the scope of the direct examination. I will withdraw it.**

:10:38 **THE WITNESS: I shall now.**

:10:39 **BY MR. DAIGNAULT:**

:10:40 Q. **Yes.**

:10:40 A. **"Solvents with a high viscosity are likely to reduce**

collapse or crystallization of amorphous drugs by inhibiting viscous flow during the formation of the cake."

Q. And, again, in Ni, in her Table 1, pointed out that TBA, among the four solvents, had the highest viscosity; isn't that right?

A. Among the four solvents that she had in Table 1, but they are -- there's only four solvents there.

Q. And if you could turn to the sentence above, it begins, "Solvents with high vapor pressures."

A. Sorry. Yes.

Q. And it says, "Solvents with high vapor pressures sublime rapidly and thus accelerate the freeze-drying process."

Do you see that?

A. That's what it said.

Q. And TBA among the four solvents disclosed in Ni had the highest vapor pressure; isn't that right?

A. It does, yes.

Q. And I just want to make sure. Let's take a look at the next sentence. I don't know if this is within the scope of your testimony or not.

It says that the cooling produced by rapid sublimation also helps to prevent the collapse of the cake by helping to keep the temperature of the cake below the collapse temperature?

:12:30 **THE COURT: Do you have an objection?**

:12:31 **MR. WIESEN: Objection. It's beyond the scope.**

:12:32 **THE COURT: I think it is, Mr. Daignault.**

:12:35 **BY MR. DAIGNAULT:**

:12:35 Q. **So, Dr. Welton, I just want to be clear. You're not looking at other attributes that solvents contribute to, other attributes or characteristics or advantages that a co-solvent may bring to a pre-lyophilization solution, is that right, except for stability?**

:12:53 A. **No, you're incorrect.**

:12:56 Q. **Well, do you have an understanding of the advantages of sublimation rate, for example?**

:13:01 A. **So you asked me if I was only considering the stability in solution. No, I'm not only considering stability in solution. There are other factors, very complex factors involving how solvents interact with solubility, so to change the reactivity level in considering all things like the concentration limits in solution.**

:13:24 **So that's not the only thing I was considering in solution, but I'm not considering, I've not been asked to consider any evidence I've given today about these things which are subsequent to the introduction of the lyophilization to the lyophilizer.**

:12:37 Q. **But are also characteristic of solvents. Right? Certain solvents have a certain sublimation rate, a vapor**

:13:24 **pressure, a freezing point, a freezing rate?**

:13:26 A. **They do, indeed. And this list of four solvents that**

:13:30 **you refer me to is just four solvents. And there are many**

:13:35 **solvents that will have different properties that are**

:13:38 **outside of the range of that table.**

:13:39 Q. **But those properties I mentioned, the sublimation**

:13:43 **rate, freezing point, vapor pressure and others that we may**

:13:49 **see in other documents, those are characteristics of certain**

:13:52 **solvents. Right?**

:13:56 A. **Every liquid will have its vapor pressure. Every**

:14:01 **liquid will have -- well, if it freezes, classically, every**

:14:06 **liquid will have a freezing point. Some of them will have a**

:14:09 **thing called a glass transition, but I don't think we need**

:14:12 **to have to worry about that here.**

:14:14 **Every liquid will have a boiling point as long**

:14:16 **as it doesn't decompose before the temperature of its**

:14:20 **boiling, which some liquids do. These are properties of**

:14:22 **liquids.**

:14:22 Q. **Right. And a person of ordinary skill in the art**

:14:26 **would consider various reasons for using a solvent in a**

:14:30 **pre-lyophilization solution. Isn't that right?**

:14:32 A. **I am sure they would, yes.**

:14:34 Q. **Dr. Welton, would it be fair to say that a person of**

:14:54 **ordinary skill in the art who is considering the use of TBA**

:14:58 **as compared to the other solvents mentioned would have had a**

:15:03 **reasonable hypothesis that because of TBA's high vapor**
:15:08 **pressure, that would lead to rapid sublimation and**
:15:10 **acceleration of the freeze-drying process?**
:15:15 A. **Can you restate that? I don't think that's about the**
:15:20 **solution.**
:15:20 Q. **Would it be fair to say that a person of ordinary**
:15:26 **skill in the art who is considering the use of TBA in a**
:15:31 **pre-lyophilization solution as compared to other solvents**
:15:35 **mentioned would have had a reasonable hypothesis that**
:15:41 **because of TBA's high vapor pressure, that would have led to**
:15:45 **rapid sublimation and acceleration of the freeze-drying**
:15:49 **process?**
:15:49 A. **Oh, yes, that is a reasonable hypothesis.**
:16:00 Q. **Do you believe that persons of ordinary skill in the**
:16:04 **art also consider cake quality in deciding what co-solvent**
:16:16 **to use? Or is that outside of what you are testifying about**
:16:20 **here today?**
:16:20 A. **You have to ask somebody else about that.**
:16:23 **MR. WIESEN: I think that is outside the**
:16:29 **testimony this witness gave.**
:16:35 **THE COURT: Sustained.**
:16:44 **BY MR. DAIGNAULT:**
:16:45 Q. **Let's take a look at Table 3, which I believe you**
:16:49 **addressed in your direct examination. I want to make sure I**
:16:52 **get this right. When we were at our deposition I called**

:16:57 **something a figure rather than table. You explained to me**
:16:59 **in science, table is above and figure is below?**
:17:02 A. **So table is the table, the list.**
:17:05 Q. **So let's take a look at Table 3, please. So here, Ni**
:17:18 **is disclosing various solvent systems. Right?**
:17:24 A. **Yes, she is.**
:17:24 Q. **Acetic acid, HAc?**
:17:29 A. **Yes, acetic acid.**
:17:31 Q. **Dimethylsulfoxide?**
:17:32 A. **Yes.**
:17:33 Q. **MeOH?**
:17:34 A. **That is methanol, which is in the table.**
:17:41 Q. **And water?**
:17:44 A. **Water.**
:17:44 Q. **And then various concentrations of TBA and water.**
:17:48 **Right?**
:17:48 A. **Yes, and pure TBA itself.**
:17:51 Q. **So she is disclosing here a 20 percent TBA and water**
:17:56 **solvent system, a 50 percent TBA-water system, 80 percent**
:18:02 **TBA-water system, and pure TBA. Is that correct?**
:18:05 A. **That's what she has got there.**
:18:06 Q. **And so she is saying here that the SarCNU is degrading**
:18:17 **faster in a hundred percent water solution as compared to a**
:18:21 **20 percent TBA and water solution. Isn't that right?**
:18:27 A. **It's degrading faster than all of the TBA-water and**

:18:31 **pure TBA -- no, it's the second fastest one there.**

:18:41 Q. **So there is a reduction in degradation in the 20**

:18:47 **percent solution as compared to water. Right?**

:18:49 A. **Yes.**

:18:49 Q. **And then when you compare the 50 percent TBA and water**

:18:57 **solution, there is reduced degradation as compared to the 50**

:19:00 **percent TBA and water solution as compared to the 20**

:19:03 **percent. Isn't that right?**

:19:04 A. **Yes, that's correct.**

:19:05 Q. **And the same holds true with the 80 percent solution**

:19:11 **compared to 50. Right?**

:19:12 A. **Indeed. And then on to the pure TBA itself.**

:19:16 Q. **So what this shows is that there is a relationship**

:19:19 **between the concentration of TBA and water and stability of**

:19:24 **the SarCNU. Right?**

:19:26 A. **Yes, it does show that there is a relationship.**

:19:29 Q. **So you would agree, Dr. Welton, that if a person of**

:19:35 **ordinary skill in the art were to lyophilize bendamustine**

:19:39 **hydrochloride, then Ni is teaching a person of ordinary**

:19:41 **skill in the art that TBA could be an acceptable solvent in**

:19:46 **pre-lyophilization solution. Isn't that correct?**

:19:51 A. **Yes, it's one of the available alternatives, yes.**

:19:55 Q. **Let's turn to DTX-999, which is the Teagarden**

:20:06 **reference. Do you have that?**

:20:26 A. **Yes.**

:20:26 Q. **Let's take a look at the abstract. You have an**
:20:32 **understanding, Dr. Welton, that TBA -- Teagarden in the**
:20:36 **abstract is discussing advantages and disadvantages of**
:20:42 **nonaqueous co-solvent systems. Is that right?**
:20:45 A. **I would have to read it again, but, yes, I believe**
:20:47 **that's the case.**
:20:48 Q. **You would agree, Dr. Welton, that a person of ordinary**
:20:57 **skill in the art in 2005 would have had the experience and**
:21:02 **skills and knowledge coming from the prior art to take into**
:21:07 **consideration the different advantages and disadvantages of**
:21:10 **using nonaqueous co-solvent systems in the freeze-drying**
:21:15 **process. Isn't that right?**
:21:17 A. **Yes. The reason they would be reading this paper is**
:21:20 **to understand what Teagarden says about them.**
:21:24 Q. **Then Teagarden says that the co-solvent system that**
:21:28 **has been most extensively evaluated was the tert-butanol-**
:21:32 **water combination. Do you see that sentence?**
:21:35 A. **That is what Teagarden says.**
:21:36 Q. **And you don't have any reason to disagree with that**
:21:45 **statement. Isn't that right?**
:21:47 A. **So I haven't conducted an independent literature**
:21:50 **search of this statement. So I have no strong evidence on**
:21:55 **which to believe that it is incorrect. But I do know that**
:22:00 **the Teagarden review is not comprehensive.**
:22:03 Q. **But a person of ordinary skill in the art reading this**

:22:06 **Teagarden reference in 2005 could reasonably believe to him**
:22:11 **or herself that the co-solvent system that has been most**
:22:15 **extensively evaluated was the tert-butanol-water**
:22:20 **combination. Isn't that a fair takeaway learning from the**
:22:24 **Teagarden disclosure?**
:22:25 A. **Only if they were accepting it on face value.**
:22:29 Q. **But that is what Teagarden says. Right?**
:22:31 A. **That's what Teagarden says, yes.**
:22:32 Q. **Now, let's take a look at Table 1 of Teagarden. So**
:22:55 **Teagarden is talking about various properties of a few**
:23:01 **solvents. Do you see that?**
:23:04 A. **I see that, yes.**
:23:05 Q. **And if we could take a look at the first five or so**
:23:15 **solvents, Mr. Vaughn, at the top of that list.**
:23:38 **So here Teagarden is reiterating some of the**
:23:44 **disclosures in the Ni reference that we saw earlier. Right?**
:23:50 A. **Some of these do appear, yes.**
:24:10 Q. **Right. She's comparing and taking a look at vapor**
:24:21 **pressure, freezing point, boiling point, flammability in**
:24:25 **water, the solvents; right?**
:24:26 A. **Those are the things that are listed.**
:24:28 Q. **And so TBA is a hundred percent soluble in water;**
:24:31 **right?**
:24:31 A. **Yes.**
:24:33 Q. **And that would be something to consider in developing**

a co-solvent system with water; right? That TBA is a hundred percent soluble in water?

A. That would depend on the concentration that you wanted it to get to. If you were only interested in having it in ten percent, it wouldn't matter if it's something soluble in 20 percent. It depends on what you -- what you want.

Q. Right. Again, a person of ordinary skill in the art could evaluate solubility with different concentrations of TBA in water; right?

A. Oh, yes. Yeah.

Q. So we talked about vapor pressure. What about freezing point? Teagarden mentions the freezing point of TBA.

Do you see that?

A. Yes, I do.

Q. And because TBA's freezing point is actually higher than water, isn't it correct that in certain concentrations, TBA can actually increase the freezing point of water?

A. Yes. Increase freezing point of water.

Q. Because TBA has a higher freezing point than water; right?

A. But it's not particularly, it's not necessarily related to -- hang on. Can I just stop a second and check something?

Q. Sure.

:26:05 A. **When you add it to water, the melting point goes**
:26:08 **down.**
:26:09 Q. **No. We're talking about freezing point.**
:26:11 A. **The freeze goes point and the melting point are**
:26:14 **different expressions of the same thing.**
:26:16 Q. **Okay. I'd like to talk about, just sort of apples and**
:26:20 **apples, talking about freezing points.**
:26:21 **So when you add TBA, which has a higher freezing**
:26:25 **point than water --**
:26:26 A. **Water ordinarily freezes at naught degrees Celcius.**
:26:32 Q. **Right.**
:26:32 A. **If you add something to it, you depress that, which is**
:26:35 **why -- this is why you put salt on snow at Christmas,**
:26:39 **because it lowers the freezing point.**
:26:42 Q. **Right. But one of the things that TBA, one of the**
:26:49 **advantages of TBA is its high freezing point; isn't that**
:26:52 **right?**
:26:53 A. **So the high/low, it's relative here. You could have**
:27:04 **something that had a, extremely high -- we talk about salt.**
:27:07 **Salt reduces the, the freezing point of water. If you want**
:27:13 **to have that effect, then it can be very high, but there are**
:27:18 **other things that you want your liquid to be able to do.**
:27:21 **You want it to, you know, be liquid without having to heat**
:27:24 **it up to 801 degrees, and so you then want its freezing**
:27:30 **point to be lower. And so there's a range in which you**

:27:33 **might like it to be.**

:27:34 Q. **Right. But as compared to ethanol, for example, which**

:27:38 **has a freezing point of negative 114 degrees Celcius to**

:27:44 **TBA's freezing point of 24 degrees Celcius, TBA's freezing**

:27:49 **point of 24 degrees Celcius is more advantageous than**

:27:57 **ethanol's negative 114 freezing point for the purposes**

:28:02 **of preparing a pre-lyophilization solution; isn't that**

:28:05 **correct?**

:28:05 A. **That could be -- yes, if you have very low freezing**

:28:10 **points, there can be technical difficulties later on in the**

:28:13 **lyophilization process.**

:28:14 Q. **And if we could take a -- again, I think Ni talked**

:28:37 **about low toxicity, sublimation rate. Those are some of**

:28:41 **those same things that are reiterated in Teagarden; is that**

:28:46 **right?**

:28:46 A. **So, yes. Yes. Not in low toxicity mentioned here.**

:28:52 Q. **Right.**

:28:52 A. **Sorry. It does lyophilize.**

:28:56 Q. **Now let's take a look at Table 2. I believe, Dr.**

:29:16 **Welton, there are 17 drug preparations listed in Table 2;**

:29:20 **is that right?**

:29:20 A. **I will agree with that count.**

:29:23 Q. **And eight of those drug preparations involve the use**

:29:27 **of TBA; isn't that right?**

:29:28 A. **Yes, that's correct.**

:29:30 Q. **And TBA is shown in different concentrations with**
:29:34 **water; is that right?**
:29:35 A. **Yes, that's correct.**
:29:36 Q. **And so all of these drugs have different chemical**
:29:43 **structures to them; isn't that right?**
:29:44 A. **They do indeed, yes.**
:29:48 Q. **And so for these different, different chemical**
:29:51 **compounds, TBA is used as a, in the solvent system in eight**
:30:01 **of these 17 compounds in Table 2; is that right?**
:30:06 A. **Yes. Actually, the preparations in this table,**
:30:09 **yes.**
:30:10 Q. **Now, I believe on your direct examination, Dr. Welton,**
:30:40 **you were shown a product, which has a very long chemical**
:30:46 **name -- maybe this is the one you were, you didn't want to**
:30:49 **mention.**
:30:50 **It's at Page 117, Mr. Vaughn, on the right-hand**
:30:56 **side. So it's below the chart. It's the presence of**
:31:03 **various levels of organic solvent can have a profound**
:31:06 **effect.**
:31:06 **Do you see that? And it's on the you right-hand**
:31:12 **side, the presence of. Right.**
:31:17 **Actually, and you were talking about this**
:31:19 **compound here. What is this compound?**
:31:24 A. **It's one of the compounds that I showed a picture of**
:31:33 **earlier on.**

:31:35 Q. **And a co-solvent system for that particular product**
:31:38 **was ethanol in water; right?**
:31:39 A. **It was indeed.**
:31:41 Q. **Right. After that discussion of this drug with**
:31:43 **ethanol in water as a co-solvent system, can you read that**
:31:46 **sentence that begins, however?**
:31:48 A. **Hang on. I just lost my place.**
:31:54 Q. **Sorry. It's the last sentence in the, the**
:31:57 **second-to-last sentence, however.**
:31:58 A. **Oh. However, Alprostadil has been successfully**
:32:04 **freeze-dried from a tert-butanol water solution, but that's**
:32:08 **a different compound.**
:32:09 Q. **And a different solvent system?**
:32:10 A. **And a different solvent system, yes.**
:32:13 Q. **And the first solvent system was ethanol in water and**
:32:16 **there were some problems; right?**
:32:17 A. **Yes.**
:32:18 Q. **And here, Teagarden is saying, however, so for**
:32:22 **Alprostadil, it has been successfully freeze-dried from a**
:32:30 **tert-butanol in water solution; is that right?**
:32:32 A. **That's absolutely what it says, yes.**
:32:58 Q. **And Teagarden explains when the drug is held in**
:33:09 **solution phase, it can experience various levels of**
:33:12 **degradation which are dependent on the kinetics of the**
:33:15 **degradation mechanism; is that right?**

:33:17 A. **Can you show me where?**

:33:20 Q. **Yes. I'm trying to find that statement. Give me a moment.**

:33:24 **(Pause.)**

:33:25 **BY MR. DAIGNAULT:**

:33:26 Q. **But compounds that react with water have different reactions of rates with water?**

:33:34 A. **Yes.**

:33:34 Q. **But they react with water?**

:33:35 A. **Yes.**

:33:36 Q. **That's hydrolysis?**

:33:37 A. **Yes.**

:33:38 Q. **And so, again, you can set up a study to assess stability and degradation rate with various concentrations of co-solvent; is that right?**

:33:50 A. **You can set up that experimental protocol, yes.**

:33:56 Q. **And Teagarden goes on to talk about trecetilide fumarate; right?**

:34:18 A. **He does, yes.**

:34:21 Q. **And that next page on 118, many would it be the sentence that has use of tertiary butyl alcohol?**

:34:46 **Can you read that sentence, Dr. Welton?**

:34:48 A. **I can indeed.**

:34:49 **"Use of tertiary butyl alcohol as a co-solvent showed solution state degradation by a factor of**

:34:52

:34:55 **approximately four to five." For that compound, obviously.**

:34:59 Q. **And then the next sentence, please?**

:35:05 A. **"This significantly increased the probability of being able to scale up the manufacturing process while maintaining tight control of the level of degradation."**

:35:17 Q. **So, again, during the course of a formulator's work in assessing stability, they would vary concentration of TBA in water and then come to a determination of which concentration would be appropriate for manufacturing scale-up and controlling degradation; is that right?**

:35:37 A. **Well, they could vary the concentration of all sorts of different solvents in water to determine whether you've got, say, rate of degradation that's acceptable to the process. TBA is one of the available alternatives, yes.**

:35:52 Q. **And Teagarden also said that the rate constant K for drug degradation was decreased substantially as the tert-butanol content was increased; right?**

:36:06 A. **In this case, it was, yes.**

:36:07 Q. **If you could look at the column over, Mr. Vaughn, that last sentence that begins, "This type."**

:36:21 **Now, Teagarden says, "This type of effect would be expected to be observed for many other drug products which are degraded in the presence of water."**

:36:29 **Do you see that?**

:36:30 A. **I do see that sentence.**

:36:31 Q. **And Teagarden is talking about the effect of increased**
:36:34 **concentration of degradation -- sorry, increased**
:36:37 **concentration of TBA and reduced degradation; is that right?**
:36:40 **MR. WIESEN: I'm going to object if he's not**
:36:41 **going to blow up the entire quote so we can see the context,**
:36:45 **your Honor. It was part of the cross-examination of Dr.**
:36:48 **Kwan yesterday.**
:36:51 **MR. DAIGNAULT: There's redirect.**
:36:53 **THE COURT: There is. Go ahead.**
:36:57 **THE WITNESS: So I can confirm that that is what**
:36:59 **that sentence says.**
:37:00 **BY MR. DAIGNAULT:**
:37:03 Q. **The question -- I think we have it.**
:37:06 **THE COURT: All right.**
:37:07 **BY MR. DAIGNAULT:**
:37:12 Q. **So now, Dr. Welton, a POSA reading Teagarden's**
:37:19 **discussions of TBA's stability -- sorry. I will rephrase.**
:37:29 **Just -- yes. So a person of ordinary skill in**
:37:45 **the art reading TBA's discussion, reading Teagarden's**
:37:47 **discussion of TBA and stability, which begins on the**
:37:51 **previous page and ends at that paragraph we saw, it would be**
:37:56 **fair to say that a person of ordinary skill in the art would**
:37:59 **believe that this type of effect of the increasing**
:38:01 **concentration of TBA and decreasing drug degradation could**
:38:06 **be expected to be observed if other drug products that are**

degraded in the presence of water. Isn't that correct?
A. Can you say that again, counsel, please?
Q. Dr. Welton, perhaps it would help if I referred you to your deposition.
A. That's fine. Just --
Q. It's --
A. I want to make sure I understood what you were saying.
MR. WIESEN: Objection, your Honor. Improper.
THE COURT: Sustained. You can ask the question, Mr. Daignault.
MR. DAIGNAULT: I will try it again.
BY MR. DAIGNAULT:
Q. A person of ordinary skill in the art reading Teagarden's discussion of TBA and stability, which begins on the previous page and ends in the sentence that we're talking about, it will be fair to say that a person of ordinary skill in the art would believe that this type of effect, increasing the concentration of TBA and decreasing drug degradation, could be expected with other drug products that are degraded in the presence of water; isn't that right?
A. So I think that they would know that it's a possibility. As we say, could not definitely expect it. They would know that it's a possibility that was worth

:39:25 **exploring amongst a number of available alternatives.**

:39:02 Q. **So a pharmaceutical formulator reading Teagarden and**

:39:22 **Ni would have had a reason to use TBA as a co-solvent in**

:39:26 **preparing a pre-lyophilization solution of bendamustine.**

:39:30 **Isn't that correct?**

:39:32 A. **So, yeah. What is correct is that once they have**

:39:36 **tried an anhydrous system and discovered the anhydrous**

:39:40 **system doesn't work for them, then they would know that**

:39:43 **using TBA with water is one of the available alternatives**

:39:47 **that they might try.**

:39:48 Q. **And based on the teachings in Teagarden and Ni, which**

:39:55 **show that increased concentration of TBA leads to improved**

:40:00 **drug stability, a person of ordinary skill in the art using**

:40:05 **TBA as a co-solvent in a pre-lyophilization solution with**

:40:10 **bendamustine hydrochloride would have a reasonable**

:40:13 **hypothesis that as you increase the concentration of TBA,**

:40:19 **the stability of bendamustine would improve. Isn't that**

:40:25 **correct?**

:40:26 A. **I think that the statement, the increasing**

:40:30 **concentration of TBA leads to decreasing decomposition of**

:40:40 **bendamustine, would constitute a reasonable hypothesis, yes.**

:40:42 **MR. DAIGNAULT: Your Honor, a moment?**

:40:52 **THE COURT: Yes.**

:40:54 **(Pause.)**

:41:14 **MR. DAIGNAULT: That's all for now, Your Honor.**

THE COURT: Thank you, Mr. Daignault.

Mr. Wiesen, redirect.

REDIRECT EXAMINATION

BY MR. WIESEN:

Q. **Very briefly.**

Dr. Welton, Mr. Daignault just asked you about whether something would be a reasonable hypothesis. Do you recall that testimony?

A. **Oh, yes, it was very recent.**

Q. **I think you are a strict applicant of the scientific method. Could you just explain to the Court what you mean when you say something is a reasonable hypothesis?**

A. **So a reasonable hypothesis is a statement, not a question, it's a statement that matches the available information and is testable by experimentation.**

Q. **And does something being a reasonable hypothesis say anything about what the likely result is of that testing of the statement?**

A. **No, no. The reasonableness of a hypothesis is how amenable to testing by experiment it is, not what the likely outcome is.**

Q. **So by the statement, the question and answer you just had with Mr. Daignault, did you mean to suggest that the person of ordinary skill in the art would reasonably expect --**

:42:43 **MR. DAIGNAULT: Objection. Leading.**

:42:44 **THE COURT: Rephrase.**

:42:45 **MR. WIESEN: I will withdraw the question, Your Honor.**

:42:47 **No further questions.**

:42:47 **THE COURT: Doctor, thank you very much. Safe travels back home.**

:42:48 **THE WITNESS: Thank you.**

:42:53 **(Witness excused.)**

:42:55 **(Recess taken.)**

:03:02 **MR. MITROKOSTAS: Good afternoon, Your Honor. Nick Mitrokostas from Goodwin Procter on behalf of plaintiff Cephalon.**

:03:06 **Plaintiff Cephalon calls as its next witness Gary Glick.**

:03:08 **... GARY D. GLICK, having been duly sworn as a witness, was examined and testified as follows ...**

:03:26 **THE COURT: Good afternoon, Dr. Glick.**

:03:44 **THE WITNESS: Good afternoon, Your Honor.**

:03:48 **MR. MITROKOSTAS: Thank you, Your Honor.**

:04:02 **THE COURT: All right, Mr. Mitrokostas.**

:04:06 **MR. MITROKOSTAS: Your Honor, Dr. Glick will be responding to Dr. Jarosz's opinions on derivation and the on-sale bar issue and relating to the on-sale bar issue experimental use. And he will also be addressing the nexus**

:04:08

:04:10

:04:15

:04:19

issue relating to secondary considerations of non-obviousness.

THE COURT: Okay. Thank you.

DIRECT EXAMINATION

BY MR. MITROKOSTAS:

Q. Good afternoon, Dr. Glick.

A. Good afternoon.

Q. Can you please introduce yourself to the Court?

A. My name is Gary D. Glick.

Q. Where are you currently employed?

A. At the University of Michigan in Ann Arbor.

Q. What is your title at the University of Michigan, Dr. Glick?

A. I am the Werner E. Bachman Collegiate Professor of Chemistry in the College of Literature, Science and Arts. And I am also a professor of biological chemistry at the University of Michigan Medical School.

Q. For how long have you been a professor at the University of Michigan?

A. 25 years.

Q. Generally, what are your responsibilities as a professor at the University of Michigan?

A. Teaching, research and service to the academic community.

Q. What is the general subject matter of the courses that

you have taught over the years?
A. I have taught organic chemistry at the undergraduate level, just a general course. I have taught synthetic organic chemistry, which is a course on how to make molecules, to graduate students.

I have taught courses on what's called physical organic chemistry to graduate students that involves understanding the reactions and kinetics, mechanisms of kinetics of organic reactions.

I have taught courses on drug discovery, and courses on pharmacology, and courses, most recently, on entrepreneurial activities in the biotech industry.

Q. Do you have a research lab at the University of Michigan?
A. Yes, I do.
Q. Over the course of your career, approximately how many graduate and postgraduate students have you trained in your laboratory?
A. In any given year, it varies between six and 15 undergraduates, graduates, Ph.D.'s or M.D.'s.
Q. Have any of those students gone on to the pharmaceutical industry?
A. The majority of them have gone on to take positions in the pharmaceutical industry.
Q. You understand that this case involves lyophilized

:06:17 pharmaceutical products and that technology. Correct?
:06:19 A. Yes, I do.
:06:20 Q. When did you first use lyophilization?
:06:21 A. In 1984 as a graduate student.
:06:23 Q. Does your laboratory use lyophilization?
:06:27 A. Yes, we do.
:06:29 Q. Can you give some examples of the ways in which you
:06:32 have used lyophilization over your career?
:06:34 A. We have used lyophilization in two principal areas.
:06:38 First, during the synthesis of potential drug molecules or
:06:42 synthetic molecules to remove water from those preparations.
:06:46 And then to prepare lyophilized compositions of drugs
:06:52 usually for pharmacology experiments in animals.
:06:55 Q. Let's just take a quick step back for a moment and
:06:58 focus on your educational background. Can you provide a
:07:01 brief description of your education?
:07:02 A. I received a Bachelor of Arts degree in 1983 from
:07:06 Rutgers University in New Jersey. I received a Master of
:07:10 Arts degree in 1984 from Columbia University. I received a
:07:14 master of philosophy degree in 1987 from Columbia
:07:18 University. A Ph.D. degree from Columbia University in
:07:22 1988. And from 1988 to 1990 I was an NIH postdoctoral
:07:28 Fellow at Harvard University.
:07:29 Q. In what subject matter did you receive your
:07:32 undergraduate and graduate degrees?

:07:33 A. **My undergraduate degree was in chemistry. And my**
:07:37 **graduate degree was in organic chemistry.**
:07:39 Q. **You mentioned that after you completed your graduate**
:07:49 **studies you did a postdoctoral fellowship at Harvard?**
:07:51 A. **Yes.**
:07:51 Q. **What did your research focus on during your**
:07:54 **postdoctoral fellowship?**
:07:55 A. **I was trying to discover at Harvard new medicines that**
:07:59 **would fight the influenza virus.**
:08:00 Q. **What did you do after you completed that fellowship?**
:08:03 A. **I took my faculty position as an assistant professor**
:08:06 **at the University of Michigan.**
:08:07 Q. **Now, aside from your professional academic experience,**
:08:12 **do you have any experience in the pharmaceutical industry?**
:08:14 A. **Yes, I do.**
:08:15 Q. **Can you give us a brief explanation of some of the**
:08:19 **experience you have had in the pharmaceutical industry?**
:08:21 A. **Over the course of my 25 years at Michigan, first I**
:08:25 **served as a consultant to a wide range of large pharma and**
:08:29 **biotech companies, and I am the founder -- I have been the**
:08:31 **scientific and business founder for venture-backed biotech**
:08:37 **companies.**
:08:37 Q. **What are the names of those companies, Dr. Glick?**
:08:41 A. **Lycera Corporation, JBR Phrama, IFM Therapeutics, and**
:08:46 **First Wave Biopharma.**

:08:48 Q. **You mentioned that these four pharmaceutical companies**
:08:50 **are venture-backed pharmaceutical companies?**
:08:52 A. **Yes.**
:08:52 Q. **Is there any significance to your opinions in this**
:08:56 **case that these companies you founded were venture-backed**
:08:59 **pharmaceutical companies?**
:09:00 A. **Yes, there is.**
:09:00 Q. **Can you explain what that significance is?**
:09:03 A. **So venture-backed companies face very unique business**
:09:07 **challenges and challenges in their development programs**
:09:12 **compared to large pharmaceutical companies. Since those**
:09:17 **companies were, a lot of my companies were funded very**
:09:22 **similar to the way that Salmedix was funded, it gives me**
:09:26 **appreciation of the R&D and business considerations that**
:09:29 **Salmedix faced.**
:09:30 Q. **Just to be clear, did you continue to serve as a**
:09:32 **professor at the University of Michigan at the same time you**
:09:35 **were founding these companies?**
:09:37 A. **So the answer is sort of. There are conflict rules,**
:09:43 **obviously, at the university that prevent me from having**
:09:47 **multiple full-time positions. So in order to satisfy,**
:09:52 **fulfill my obligations to the university and to the**
:09:54 **companies, I would either take a leave of absence, I have**
:09:57 **used sabbatical mechanisms, and at various times I have used**
:10:01 **reduced appointments at the university.**

:10:02 Q. **At any of the companies that you have founded, have**
:10:05 **you had any responsibilities for making regulatory decisions**
:10:11 **relating to the products that they are working on?**
:10:15 A. **Just to step back for a second, when one is interested**
:10:18 **in developing a drug, one needs to think about the final**
:10:24 **product, the drug molecule, that one is interested in**
:10:26 **making. You need to understand how that drug is going to be**
:10:30 **administered, is it a chronic indication, is it an acute**
:10:33 **indication. And as a consequence of that, one needs to**
:10:36 **understand the various regulatory strategies or plan out the**
:10:40 **regulatory strategies as you work backwards, simultaneously**
:10:44 **as you are doing the scientific strategy sort of walking**
:10:48 **forward.**
:10:48 **In my companies, at various stages, I had**
:10:51 **ultimate responsibility for making decisions regarding some**
:10:55 **of those strategies.**
:10:56 Q. **Did you have any experience in those companies again**
:10:59 **interacting with regulatory agencies like the FDA?**
:11:02 A. **Yes, I did.**
:11:03 Q. **Can you just describe some of the experience you have**
:11:05 **had?**
:11:07 A. **Sure. So I have prepared, or been part of**
:11:13 **preparations of pre-IND documents and had face-to-face**
:11:17 **meetings with the FDA. I have had followup meetings with**
:11:21 **FDA around those sorts of documents. I have interacted as**

part of those with ex-FDA regulators, intimately, in fact, in planning out regulatory strategy for those meetings. I have interacted with the European equivalent to the FDA in three different jurisdictions.

Q. Based on that experience, did you gain any knowledge regarding the requirements for obtaining FDA approval of a pharmaceutical product?

A. Yes.

Q. What general types of knowledge have you gained?

A. So through that process, I would understand, again, the types of experiments and the types of things that one would need with respect to manufacturing, clinical protocols, clinical trials and the like, in order to successfully launch, ultimately launch a product.

Q. Are you the named inventor on any United States patents?

A. Yes.

Q. Approximately how many patents are you the named inventor on?

A. I am the named inventor on 27 U.S. patents and the named inventor on about 50 applications currently pending before the U.S. PTO.

Q. Do any of those patents relate to pharmaceutical products?

A. All of them do.

:12:31 Q. **Have you received any awards for your research?**
:12:34 A. **Yes, I have.**
:12:34 Q. **Can you just give one or two examples?**
:12:38 A. **Most recently, I was named a fellow of the American**
:12:42 **Association for the Advancement of Science, American Cancer**
:12:44 **Society awards, awards from the National Science Foundation.**
:12:48 **And things like that.**
:12:49 Q. **Have you prepared a presentation to assist you with**
:12:55 **your testimony today?**
:12:56 A. **Yes, I have.**
:12:57 Q. **If you could turn to PTX-246 in your trial binder. Do**
:13:11 **you recognize this document?**
:13:15 A. **Yes.**
:13:15 Q. **What is it?**
:13:16 A. **This is the front page of my CV.**
:13:19 Q. **Does it accurately summarize your professional and**
:13:20 **educational experience?**
:13:22 A. **It is missing a couple things since I gave it to you.**
:13:26 **But it's 99 percent correct.**
:13:28 **MR. MITROKOSTAS: Your Honor, plaintiffs would**
:13:30 **like to offer Dr. Glick as an expert in the fields of**
:13:33 **organic chemistry and drug discovery and development.**
:13:36 **MR. DZWONCZYK: No objection.**
:13:37 **THE COURT: The Doctor is accepted as an expert**
:13:40 **in those fields.**

:14:06 Q. **Now, Dr. Glick, let's turn to your involvement in this**
:14:09 **case and the subject of your testimony today. If we could**
:14:14 **please have the next slide, please. All right.**
:14:20 **Dr. Glick, on what issues are you going to**
:14:22 **testify about today?**
:14:23 A. **So I will respond to Dr. Jarosz and offer the opinion**
:14:28 **that the claimed invention of the '270 patent was not**
:14:30 **derived from Fujisawa.**
:14:32 **I will also offer the opinion in response**
:14:35 **to Dr. Jarosz that Ribomustin does not anticipate the**
:14:39 **asserted claims, asserted claims of the '270 patent.**
:14:42 **And I will discuss secondary considerations**
:14:44 **of nonobviousness.**
:14:46 Q. **Were you here for Dr. Jarosz's testimony yesterday and**
:14:50 **this morning?**
:14:51 A. **Yes.**
:14:51 Q. **And did you also hear the testimony of Mr. Brittain**
:14:54 **and Dr. Kabakoff over the last few days?**
:14:58 A. **Yes, I did.**
:15:01 Q. **Now, from what perspective did you analyze these**
:15:03 **issues?**
:15:04 A. **Person of skill in the art.**
:15:05 Q. **Do you have a definition of a person of ordinary**
:15:07 **skill in the art as it relates to the patents in this**
:15:10 **case?**

:15:10 A. **Yes, I do.**

:15:11 Q. **All right. And if we could turn, please, to slide PDX-7-4.**

:15:17 **Dr. Glick, can you explain the definition that you have put forward for the person of ordinary skill in the art?**

:15:23 A. **So a person of skill in the art related to this case would be an individual with a Bachelor's degree in pharmaceutical sciences or a related field such as chemistry, at least five years of experience formulating, characterizing, or analyzing pharmaceutical compositions.**

:15:40 **The individual could also have a Master's or doctoral degree in pharmaceutical-related sciences, and at least three years of experience in formulating, characterizing or analyzing pharmaceutical products.**

:15:52 **This person would, and as is common in the pharmaceutical industry, would have access to and collaborate, if they need, with individuals in other areas of science, including medicine and drug development.**

:16:07 Q. **Are you aware that defendants' experts have put forward other definitions for the person of ordinary skill in the art?**

:16:13 A. **Yes.**

:16:14 Q. **Did you consider those alternative definitions?**

:16:16 A. **Yes, I did.**

:16:16 Q. **And would any of your opinions and the testimony that**
:16:18 **you are going to give today change if the Court were to**
:16:21 **adopt one of those other definitions?**
:16:23 A. **No. My opinions wouldn't change regardless of the**
:16:25 **definition.**
:16:26 Q. **Now, Dr. Glick, I'd like to turn to the first issue,**
:16:30 **your response to the arguments made by Dr. Jarosz on**
:16:33 **derivation. If we can please have the next slide.**
:16:39 **So, Dr. Glick, did you hear Dr. Jarosz testify**
:16:42 **that the claimed inventions of the '270 patent were derived**
:16:46 **from work done by Fujisawa on Ribomustin because the**
:16:50 **inventors received information from Fujisawa?**
:16:54 A. **Yes, I did.**
:16:54 Q. **Do you agree with Dr. Jarosz?**
:16:57 A. **No, I do not agree.**
:16:58 Q. **And just to be clear, you heard Dr. Jarosz testify**
:17:02 **that his opinion applies only to Claims 19, 20 and 21 of,**
:17:06 **only the '270 patent; is that right?**
:17:09 A. **That is correct.**
:17:10 Q. **If we could please take a look at Claim 19 of the '270**
:17:14 **patent, which is JTX-5, and this is on PDX-7-6.**
:17:23 **Dr. Glick, does Claim 19 depend on any other**
:17:29 **claim?**
:17:29 A. **Claim 19 in the '270 patent depends on Claim 7.**
:17:32 Q. **And have you prepared a slide showing claim 19**

:17:36 **rewritten in independent form to include the limitations of**
:17:39 **Claim 7?**
:17:39 A. **Yes, I have.**
:17:40 Q. **Is that Claim 7? I apologize. All right. If we**
:17:43 **could take a look at the next slide, please, which is**
:17:45 **PDX-7-7.**
:17:47 **What does claim 19 cover?**
:17:49 A. **"A pharmaceutical composition of bendamustine**
:17:52 **hydrochloride containing less than or equal to four percent**
:17:55 **(area percent of bendamustine) of bendamustine degradants,**
:18:02 **containing not more than about 0.5 percent area percent of**
:18:07 **bendamustine of a compound of Formula 4."**
:18:09 Q. **Now, do you understand that derivation requires that**
:18:14 **the information provided to the inventors would have enabled**
:18:14 **them to practice the claimed invention?**
:18:16 A. **Yes, I do.**
:18:17 Q. **Did the documents and information provided by Fujisawa**
:18:21 **to the inventors enable them to make the composition of**
:18:23 **Claim 19?**
:18:24 A. **No, they did not.**
:18:25 Q. **Generally speaking, why not?**
:18:26 A. **Documents that were transferred to Fujisawa, from**
:18:31 **Fujisawa to Salmedix only provided the ability to make the**
:18:36 **Fujisawa, the compositions of Fujisawa to the Fujisawa**
:18:40 **specification, which is different than what Mr. Brittain**

invented.

Q. **All right. Let's first turn to one of the documents that Dr. Jarosz relied on, which is JTX-128-A.**

And do you recognize this document, Dr. Glick?

A. **Yes, I do.**

Q. **And generally speaking, what is this document?**

A. **This is the Fujisawa Deutschland common technical document, and this section specifically relates to the manufacture of the drug product.**

Q. **And does this document contain information regarding the specification of impurities in Fujisawa's Ribomustin product?**

A. **Yes, it does.**

Q. **All right. And, generally, what is the relationship between the impurity levels in Ribomustin described here in this document and the claimed impurity levels in the '270 patent?**

A. **The claimed impurity levels, or the specification rather for the impurity levels here are greater than what is in the claimed invention.**

Q. **Let's go to the specification first, and that appears on Page 1680812, which is PDX-7-9 in JTX-128.**

Do you have that, Dr. Glick?

A. **Yes, I do.**

:19:59 Q. **What is the specification for HP1 in Fujisawa's**
:20:04 **Ribomustin product?**
:20:05 A. **Less than or equal to 3.3 percent.**
:20:08 Q. **And what is the specification for BM1EE in Fujisawa's**
:20:15 **Ribomustin product?**
:20:16 A. **Less than or equal to 0.6 percent.**
:20:18 Q. **And finally, what is the specification for total**
:20:20 **impurities in Fujisawa's Ribomustin product?**
:20:23 A. **Less than or equal to 5.0 percent.**
:20:26 Q. **Have you prepared a slide that compares the impurities**
:20:30 **in the specification for Fujisawa's product with the claims**
:20:34 **of the '270 patent?**
:20:36 A. **Yes.**
:20:37 Q. **All right. I think this is slide PDX-7-10. Could you**
:20:41 **please explain what's shown on this slide?**
:20:43 A. **So in the left column going down there's an HP1, which**
:20:48 **we've heard quite a bit about so far. BM1EE, which we've**
:20:53 **heard about. Total degradants, which is all the composition**
:20:56 **products, something together.**
:20:57 **The column going down in the blue are the**
:21:00 **patent specification, the degradant specification for the**
:21:04 **'270 patent, and the red going down is the specification for**
:21:06 **Fujisawa, the Ribomustin product.**
:21:08 Q. **Now, can you explain why in your opinion the Fujisawa**
:21:12 **document cited by Dr. Jarosz did not enable Salmedix to make**

:21:18 **the invention of Claim 19 of the '270 patent?**

:21:21 A. **The material that was transferred from Fujisawa to**

:21:26 **Salmedix only taught how to make the product, the Ribomustin**

:21:31 **product to the specification shown here. It did not teach**

:21:37 **how to make the specification in the '270 patent.**

:21:41 Q. **And typically, how did the specification relate to a**

:21:44 **pharmaceutical product, Dr. Glick?**

:21:46 A. **It is the specification that defines the drug product.**

:21:50 Q. **Now, Dr. Glick, based on your review of materials from**

:21:54 **Fujisawa, are you aware of some lyophilized Ribomustin**

:21:58 **batches that contained less than four percent total**

:22:02 **impurities?**

:22:03 A. **Yes.**

:22:04 Q. **All right. Does the fact that there were batches that**

:22:07 **contained less than four percent total impurities change**

:22:10 **your opinion?**

:22:11 A. **No, it does not. I have looked at somewhere between**

:22:16 **six and ten batches that were manufactured over the course**

:22:19 **of about a year that have less than four percent degradant,**

:22:27 **but my, in my understanding of the chemistry of this**

:22:29 **molecule and given the fact that this molecule has been**

:22:34 **produced over 30-plus years, and given the fact that the**

:22:39 **specification is, as we see, less than five percent, I would**

:22:43 **find it highly unlikely that there are not other batches**

:22:47 **that have, that -- that certainly fall outside the '270**

patent specification.

Q. If we could now turn to claims 20 and 21, which appear on PDX 7-11 from JTX-5.

And, Dr. Glick, what is claimed in claims 20 and 21? If you could read it, please.

A. Claim 20 starts off saying, "A method of treating cancer in a patient comprising administering to the patient a pharmaceutical composition of bendamustine hydrochloride according to Claim 7."

And claim 21: "The method according to claim 20, wherein the cancer is chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or breast cancer."

Q. Do pharmaceutical compositions comprising bendamustine have to be prepared in any way before they're administered to patients under a method of treatment?

A. Yes. They need to be -- they need to be dissolved in a medium that is acceptable for administration to an individual, and typically, they are diluted in an IV solution for an infusion.

Q. And is that medium that you're referring to sterile water or sterile water for injection?

THE COURT: Leading.

BY MR. MITROKOSTAS:

Q. What is that medium, Dr. Glick?

:24:09 A. **The medium, where it's usually sterile in water for**
:24:12 **the initial reconstitution followed by the a saline solution**
:24:17 **for the infusion.**
:24:17 Q. **Dr. Glick, is there any impact on the HP1 level in a**
:24:25 **batch of Ribomustin once it has been reconstituted in**
:24:29 **sterile water and diluted in saline?**
:24:31 **MR. DZWONCZYK: Leading again, your Honor.**
:24:34 **THE COURT: I disagree. Overruled.**
:24:37 **THE WITNESS: Yes.**
:24:38 **BY MR. MITROKOSTAS:**
:24:39 Q. **What is that effect?**
:24:41 A. **The Ribomustin would undergo hydrolysis with water and**
:24:44 **the HP1 level.**
:24:51 Q. **And so what would you expect to happen with the batch**
:24:53 **of Ribomustin that's within the specification once it has**
:24:57 **been prepared for administration to a human patient?**
:25:00 A. **To very likely go above that specification for**
:25:03 **degradants.**
:25:04 Q. **All right. So, Dr. Glick, in your opinion, did the**
:25:08 **Fujisawa documents enable the inventors of the '270 patent**
:25:11 **to make the inventions claimed in Claims 20 and 21?**
:25:14 A. **No. As I said earlier, the Fujisawa materials only**
:25:20 **taught how to make or manufacture to the Fujisawa**
:25:22 **specification.**
:25:22 Q. **Dr. Glick, I'd now like to turn to the next issue,**

:25:25 **which is the on-sale bar issue that Dr. Jarosz testified**
:25:29 **about. And we're now on PDX-7-12.**
:25:34 **Did you hear Dr. Jarosz testify that claims 1**
:25:37 **and 19 of the '270 patent were anticipated by certain**
:25:40 **batches of Ribomustin based on the data in Table 13 of the**
:25:45 **patent?**
:25:45 A. **Yes, I did.**
:25:46 Q. **Do you agree with Dr. Jarosz's opinion?**
:25:49 A. **I absolutely do not.**
:25:50 Q. **Why not?**
:25:51 A. **The -- it's very clear from all the information that I**
:25:54 **have looked at that these materials, these batches were**
:25:58 **produced solely and expressly for experimental purposes.**
:26:01 **Those are clinical trials and formulation development.**
:26:05 Q. **Is there another reason that you disagree with Dr.**
:26:08 **Jarosz?**
:26:08 A. **Well, as I indicated here, the data in Table 13**
:26:16 **clearly are not pharmaceutical compositions that have**
:26:19 **reconstituted particularly under the Court's definition of**
:26:23 **the -- of a pharmaceutical reconstitution, pharmaceutical**
:26:28 **composition.**
:26:28 Q. **All right. Before we get into the construction of the**
:26:30 **term that you used in forming your opinions, let's just take**
:26:34 **a look at Claim 1 of the '270 patent, which is PDX-7-13. It**
:26:41 **appears at JTX-5 in column 36.**

:26:44 **Dr. Glick, what's claimed in Claim 1 of the '270 patent?**

:26:49 A. **Claim 1 claims a pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9 percent (area percent of bendamustine) of HP1.**

:27:07 Q. **And you mentioned the construction that you utilized in forming your opinions. If we could go to the next slide, please, PDX-7-14.**

:27:17 **Dr. Glick, did you employ -- what is the construction of the term pharmaceutical composition that has been reconstituted in the '270 patent?**

:27:27 A. **It has been construed to mean pharmaceutical composition that has been dissolved in a solvent and that is suitable for medical administration.**

:27:36 Q. **And did you employ this construction in your analysis?**

:27:41 A. **Yes, I did.**

:27:42 Q. **And what would a person of ordinary skill in the art understand to be required by the construction?**

:27:46 A. **So first you need to dissolve the composition; and, second, that solvent needs to be suitable for administration to a patient.**

:27:55 Q. **And do you agree with Dr. Jarosz, that the data in**

Table 13 was generated from pharmaceutical compositions that have been reconstituted in accordance with the Court's construction?

A. **Absolutely not.**

Q. **Why not?**

A. **Because they were dissolved in methanol, and methanol is highly toxic and cannot be administered to patients.**

Q. **And what indicated to you that they were dissolved in methanol?**

A. **In looking at the patent, it's clear under HPLC method 3 what -- what the solvent is.**

Q. **If you could please turn to HPLC method 3, which we're now on PDX 7-16. And this is column 29, lines 3 through 31 of the '270 patent.**

Dr. Glick, what's described in method 3?

A. **So method 3 starting at the top talks about the actual HPLC protocol and the, the -- what's called the column that's used for the actual separation from the experimental parameters. One can see that listed in that table. And then highlighted in yellow describes the sample preparation.**

Q. **And what was the sample preparation that was used to analyze the batches and generate the data in Table 13 of the '270 patent?**

A. **For the sample preparation, the drug was dissolved in 200 milliliters of methanol. It was sonicated and then**

:29:29 **analyzed by injection onto the HPLC.**

:29:32 Q. **And in your opinion, are batches that have been**

:29:34 **dissolved in 200 milliliters of methanol dissolved in a**

:29:37 **solvent and suitable for medical administration?**

:29:39 A. **No.**

:29:41 Q. **Can you please provide your explanation?**

:29:43 A. **So methanol is highly toxic. We probably -- everyone**

:29:48 **in this court has heard of wood alcohol, that's methanol,**

:29:51 **and as little as four milliliters, there are reports of**

:29:56 **fatalities, blindness, things. So methanol is not something**

:30:00 **that one administers to patients. I believe Dr. Jarosz also**

:30:04 **agreed with that statement.**

:29:38 Q. **So in your opinion, Dr. Glick, does the data in Table**

:29:45 **13 demonstrate that the Ribomustin batches meets the**

:29:48 **limitations of Claim 1?**

:29:49 A. **With respect to the Court's claim construction, the**

:29:53 **data in Table 13 has no relation to that.**

:29:56 Q. **Why don't we turn now to the next issue that you are**

:30:00 **addressing on the on-sale bar response. This is**

:30:05 **experimental use.**

:30:06 **Dr. Glick, do you have an opinion about how**

:30:09 **Salmedix used the Ribomustin batches that they received from**

:30:12 **Fujisawa?**

:30:12 A. **Yes, I do.**

:30:13 Q. **Very generally, how did Salmedix use the Ribomustin**

:30:17 lots that they obtained from Fujisawa?
:30:19 A. They used the Salmedix -- Salmedix used the batches
:30:23 they obtained from Fujisawa for, exclusively for
:30:29 experimental purposes. One of those being, one purpose
:30:32 being Phase II clinical trials, to help establish efficacy
:30:35 of the product suitable for the FDA, and the second was
:30:39 preclinical development, specifically around developing Mr.
:30:46 Brittain's new formulation.
:30:46 Q. If we could please turn to PDX-7-18.
:30:58 Dr. Glick, do you recognize this document as the
:31:00 license agreement about which Dr. Jarosz testified?
:31:03 A. Yes, I do.
:31:04 THE COURT: Counsel?
:31:05 MR. DZWONCZYK: Your Honor, I will object to the
:31:07 use of this document with this witness. First and foremost,
:31:10 it is cumulative. We have had Dr. Kabakoff on Monday who
:31:12 authored the document and signed it, negotiated the deal, we
:31:15 have heard his testimony. He has been dismissed.
:31:17 We have heard the testimony from Mr. Brittain.
:31:19 This witness, as a foundational matter, didn't participate
:31:23 in the authoring of this document. And frankly, I don't
:31:26 know what relevance he is going to offer as an
:31:28 interpretation that we have not already heard.
:31:30 THE COURT: Did Dr. Jarosz participate in the
:31:32 development of the document?

:31:33 **MR. DZWONCZYK: No. Dr. Glick.**

:31:34 **THE COURT: Dr. Jarosz, did he participate in**
:31:36 **the development of the document?**

:31:39 **MR. DZWONCZYK: He did not.**

:31:39 **THE COURT: He was offered in your side's case**
:31:43 **to discuss the document. And there was some back-and-forth**
:31:47 **about that. I disagree.**

:31:52 **MR. MITROKOSTAS: That's right, Your Honor.**

:31:54 **MR. DZWONCZYK: I think Your Honor limited Dr.**
:31:57 **Jarosz's testimony to reading statements without --**

:31:59 **THE COURT: Let's see what Mr. Mitrokostas asks.**

:32:03 **You would object to him interpreting the**
:32:05 **document and I would probably side with that.**

:32:07 **MR. DZWONCZYK: That's correct, Your Honor.**

:32:10 **BY MR. MITROKOSTAS:**

:32:11 Q. **Let's back up for a moment and focus a little bit on**
:32:13 **some of your experience with licensing agreements.**

:32:16 **As a member of the management team of**
:32:18 **venture-backed pharmaceutical companies, have you ever been**
:32:21 **involved in the preparation and negotiation of a license**
:32:23 **agreement?**

:32:24 A. **I have been directly responsible and negotiated**
:32:28 **probably well over two dozen license agreements.**

:32:31 Q. **And very generally, can you describe some of the**
:32:35 **experience you have had in negotiating and preparing a**

:32:38 **license agreement for the development of pharmaceutical**
:32:40 **products?**
:32:40 A. **So I have been on both sides of agreements such as**
:32:45 **this, and negotiating, where I have either out-licensed**
:32:49 **technology from my company to another company, and I have**
:32:52 **also been on side of the agreements where I have in-licensed**
:32:56 **technology from another company.**
:32:58 **From that perspective, I can opine on the**
:33:02 **generalities of the document.**
:33:03 Q. **All right. And have you been involved in work that**
:33:06 **was done pursuant to a license agreement for the development**
:33:09 **of a pharmaceutical product?**
:33:10 A. **So my first company, Lycera, had two very large deals**
:33:15 **with Merck, just concluded a large deal with Celgene, and**
:33:19 **early in the day we had a reasonable sized deal with Medicis**
:33:24 **Pharmaceuticals.**
:33:25 **So, yes.**
:33:25 Q. **Now, Dr. Glick, based on your experience with these**
:33:29 **types of licensing development arrangements, do you have an**
:33:32 **understanding of the nature of the relationship that's**
:33:35 **created by such an agreement?**
:33:36 A. **Yes, I do.**
:33:37 Q. **And what is your general understanding of the nature**
:33:39 **of the relationship created by a license agreement like the**
:33:43 **one between Salmedix and Fujisawa?**

A. **So this is really a collaboration between the two companies in order to develop a product. In this case, Fujisawa is transferring information and facilitating through company supplies materials to Salmedix to help commercialize a bendamustine-containing product in the United States.**

So it is a close relationship between companies.

Q. **How common are these types of agreements, particularly in venture-backed pharmaceutical companies like the companies you have had experience with, in Salmedix?**

A. **These are common in all of my companies. They are common in large pharmaceutical companies. There is nothing atypical about this agreement.**

Q. **Now, if we could please turn to Article 4 of the agreement. I don't want to ask -- I am not asking you to interpret the agreement or this provision. But this was a provision that Dr. Jarosz testified about.**

Do you recall that?

A. **Yes.**

Q. **And do you recall that he testified that the language suggested that Salmedix had commercially purchased batches from Fujisawa?**

A. **Yes.**

Q. **Do you agree?**

A. **No, I disagree with Dr. Jarosz's opinion.**

:34:53 Q. **Why do you agree with Dr. Jarosz?**

:34:56 A. **In my experience, and based on that experience broadly, it's my opinion that this is a simple reimbursement for cost of goods.**

:35:07 **And if I just may add, I have negotiated where I had provided, one of my companies had provided materials like this, and we were reimbursed for cost of goods.**

:35:17 Q. **And based on your experience with these types of agreements, do you have an opinion as to why one company would pay another company, or reimburse another company for product pursuant to a license agreement?**

:35:31 A. **There can be a number of reasons. But it's, again, to recognize, potentially to just recognize the expense that that company made.**

:35:39 **Again, the nature of this type of agreement is really to facilitate the interaction between the two parties.**

:35:44 Q. **Now, is it your understanding that this Article 4 would have been the financial consideration for the license agreement between Salmedix and Fujisawa?**

:35:55 A. **No. This has nothing to do with the actual consideration of this particular transaction.**

:36:00 Q. **Is there another provision in the agreement -- is there any other provision in the agreement that deals with financial consideration?**

:36:07 A. **So Article 6 clearly lays out the bio-bucks, if you**
:36:14 **will, for this particular transaction, including an up-front**
:36:16 **license fee that Salmedix paid.**
:36:23 **MR. DZWONCZYK: Your Honor, he appears to be**
:36:25 **interpreting the license agreement again.**
:36:32 **THE COURT: It's close. I can read it.**
:36:36 **MR. DZWONCZYK: That is my point, Your Honor.**
:36:38 **MR. MITROKOSTAS: I wanted to direct him to this**
:36:40 **page. But otherwise I have no further questions on this,**
:36:43 **Your Honor.**
:36:43 **THE COURT: Okay.**
:36:44 **BY MR. MITROKOSTAS:**
:36:45 Q. **Now, Dr. Glick, why don't we turn to the use to which**
:36:48 **the Salmedix inventors put the Ribomustin batches that they**
:36:53 **obtained pursuant to the license agreement. Generally**
:37:02 **speaking, for what purpose did the inventors use these lots**
:37:05 **of Ribomustin that Dr. Jarosz testified about?**
:37:09 A. **As I discussed a few moments ago, these lots were used**
:37:13 **in experiments, only experimental use, those being namely**
:37:17 **clinical trials and process development for formulation.**
:37:21 Q. **To be clear, what were the batches that Dr. Jarosz**
:37:25 **testified about and that you are offering your opinion**
:37:27 **about, the particular batches that he mentioned in his**
:37:30 **testimony?**
:37:31 A. **03C08, 03H07, 02K27, 03H08.**

:37:42 Q. **Have you reviewed documents that have informed you as**
:37:46 **to the fact that these batches were used for clinical trials**
:37:50 **and process development?**
:37:51 A. **Yes, I have.**
:37:51 Q. **If we could please go to PDX-7-22, which is JTX-33. I**
:38:04 **am going to -- we will start on Page 2 of this, Dr. Glick,**
:38:14 **which was -- do you recall that this was the subject of**
:38:17 **testimony by Dr. Jarosz in exchange with Mr. Ware this**
:38:22 **morning?**
:38:23 A. **Yes, I do.**
:38:23 Q. **Do you recall that Dr. Jarosz indicated that the**
:38:29 **batches on this page showed that these batches would have**
:38:33 **been used for clinical trials?**
:38:35 A. **Yes, I do.**
:38:36 Q. **In your opinion, is the use of these batches for**
:38:42 **clinical trials consistent with the license agreement?**
:38:45 A. **Yes, absolutely.**
:38:46 Q. **Can you explain how they are?**
:38:51 A. **So these are, these clinical trials are integral,**
:38:55 **obviously, to the drug discovery or development process.**
:38:59 **And the batches that were provided were used to establish**
:39:04 **the efficacy in dose range finding Phase II studies, as Dr.**
:39:09 **Kabakoff testified to, in the United States.**
:39:12 Q. **Were the batches used in the -- was the use of the**
:39:16 **batches in the clinical trial related in any way to the**

:39:19 **inventions claimed in the '270 patent?**
:39:22 A. **Yes, they were.**
:39:22 Q. **Can you explain how they are related?**
:39:25 A. **Sure. So the batches in the clinical trial need to be**
:39:31 **ultimately reconstituted and administered to a patient, and**
:39:35 **then they were used to determine whether or not efficacy of**
:39:39 **the compound was observed.**
:39:40 Q. **Now, you mentioned that these batches were also used**
:39:44 **for other purposes, such as process development. Is that**
:39:48 **right?**
:39:48 A. **That's correct.**
:39:48 Q. **And have you seen any documents that indicated that to**
:39:51 **you?**
:39:52 A. **Yes, I have.**
:39:52 Q. **If we could please go to JTX-103, which appears on**
:39:59 **PDX-7-23. Dr. Glick, what is this document?**
:40:04 A. **This is, the title of this document is Reverse Phase**
:40:08 **HPLC Analysis of Bendamustine Hydrochloride Drug Substance**
:40:12 **and Product.**
:40:14 Q. **I want to direct your attention first to the cover**
:40:17 **page, the very first page of this document. Do you see that**
:40:20 **there is a name identified on the page, J. Craig Franklin?**
:40:25 A. **Yes, I do.**
:40:26 Q. **Do you know who J. Craig Franklin is in relationship**
:40:29 **to the patents in this case?**

A. **Mr. Franklin is one of the inventors on the named patents.**

Q. **Now, what was the purpose of this method development report?**

A. **This method -- this report was meant to summarize the Salmedix methods -- or the Salmedix experiments, rather, that developed a method to determine the impurity levels in the bendamustine formulations and potentially to measure bendamustine levels and degradant levels in their clinical trials.**

Q. **Is developing an analytical method like the HPLC method here part of the drug development process?**

A. **Methods like this are integral to the drug discovery process, yes.**

Q. **If we could please turn to Page 4 of this report, Cephalon 159973. We are still in JTX-103, Dr. Glick.**

I believe it appears on PDX-7-24 as well.

Can you very generally explain what 7.1 materials describes?

A. **This is a section from the report, typically referred to as an experimental or materials and equipment section. And what's not highlighted in yellow are the various instruments that were used and the various reagents that were used in the analyses. And highlighted in yellow are the Ribomustin batches that were used during the analysis.**

:42:02 Q. **What batches were used during the HPLC analysis that**
:42:09 **was part of this method development?**
:42:11 A. **Lot 03H08 and Lot 02K27.**
:42:16 Q. **Do you know if these are some of the batches that Dr.**
:42:19 **Jarosz testified about?**
:42:20 A. **These are batches that Dr. Jarosz testified about,**
:42:23 **yes.**
:42:23 Q. **Now, how does the development of the HPLC method**
:42:29 **relate to the claimed inventions of the '270 patent, if it**
:42:33 **does?**
:42:33 A. **It allows one to be able to determine whether or not**
:42:38 **the degree of the degradant levels that are specified have**
:42:41 **been achieved.**
:42:41 Q. **Do you know whether this particular method development**
:42:46 **is in any way related to the specification of the '270**
:42:49 **patent?**
:42:51 A. **This exact method is found I think almost verbatim in**
:42:56 **the patent.**
:42:56 Q. **If we could please go to the next slide. We are now**
:42:59 **at PDX-7-25. Dr. Glick, if you could please explain what**
:43:04 **you have displayed on the slide?**
:43:05 A. **On the left of the slide is the method development**
:43:09 **report, where it is termed HPLC Method 1. On the right is**
:43:14 **Example 1 from the '270 patent. I think if you look at**
:43:17 **them, go down, everything pretty much from top to bottom, I**

:43:23 **think they are identical.**

:43:27 Q. **Dr. Glick, in your opinion, were the Batches 03H08, 03H07, 02K27, and 03C08, the four batches discussed by Dr. Jarosz, used by Salmedix for development purposes?**

:43:45 A. **Yes. These batches were used unambiguously for developmental experimental purposes.**

:43:51 Q. **Dr. Glick, I would like to turn to the last issue that you are discussing in your testimony today, which is nexus between Treanda and the claimed invention.**

:44:02 **I want to ask you some questions about the impact of the features of Treanda which are covered by the claims.**

:44:11 **Did you hear Dr. Kabakoff and Mr. Brittain testify about the development of Treanda?**

:44:17 A. **Yes, I did.**

:44:17 Q. **Based on your analysis of the patents and the testimony and documents that you have reviewed, have you formed any opinions about whether Ribomustin could have been approved by the FDA?**

:44:26 A. **Yes, I have.**

:44:27 Q. **What is your opinion?**

:44:30 A. **There is no way that Ribomustin at the time would have been approved by the U.S. FDA.**

:44:57 Q. **And why is that?**

:45:00 A. **So -- I'm sorry.**

:45:06 **MR. DZWONCZYK: Your Honor, Dr. Glick is not an**
:45:08 **expert in FDA matters or regulatory matters. He has been**
:45:12 **qualified as an expert in organic chemistry and drug**
:45:15 **formulation.**
:45:15 **THE COURT: All right. Rephrase.**
:45:19 **MR. MITROKOSTAS: Your Honor, Dr. Glick, while**
:45:21 **he has not worked at the FDA, testified that he has founded**
:45:23 **a number of companies that have been involved in making**
:45:27 **decisions on regulatory strategy; that he has communicated**
:45:30 **with FDA; that he has an understanding of the regulatory**
:45:34 **requirements as it relates to drug approval, and I think**
:45:36 **he's qualified.**
:45:38 **MR. DZWONCZYK: And he can talk about that, but**
:45:40 **to offer an opinion on this particular, this particular drug**
:45:43 **product and this particular FDA approval process is out of**
:45:46 **the scope of his expertise.**
:45:47 **THE COURT: Are you objecting to -- I think you**
:45:53 **just agreed he could offer an opinion that this is not**
:45:56 **approved by the FDA, or am I --**
:45:59 **MR. DZWONCZYK: I object to him offering that**
:46:01 **opinion. Now he's about to state the reasons why.**
:46:04 **MR. MITROKOSTAS: Your Honor, I think that Dr.**
:46:06 **Glick has the qualifications to offer an opinion, at least**
:46:10 **from the perspective of somebody in the position of**
:46:13 **Salmedix, who --**

:46:14 **THE COURT: Was it discussed in his expert report and was this the subject of deposition?**

:46:19 **MR. MITROKOSTAS: It was. It was discussed in his expert report.**

:46:21 **THE COURT: Was he deposed?**

:46:23 **MR. MITROKOSTAS: He was deposed.**

:46:24 **THE COURT: Was it an issue then?**

:46:26 **MR. DZWONCZYK: It was, your Honor. He was asked if he considered himself to be an expert in FDA matters, and he talked about his experience, that he's not saying he was an expert in FDA regulatory matters.**

:46:43 **MR. MITROKOSTAS: Your Honor, I can approach with a copy?**

:46:46 **THE COURT: No. He agrees it was discussed.**

:46:52 **MR. DZWONCZYK: We just disagree he's qualified to give an opinion on what didn't happen.**

:49:11 **THE COURT: Let's see counsel for a moment, please.**

:49:11 **(Sidebar conference held as follows.)**

:49:11 **THE COURT: All right. Restate your objection for me again. Tell me why you object.**

:49:11 **Let me do it this way. What's the question you want to ask him? What is it that you are trying to get from him regarding the FDA?**

:49:11 **MR. MITROKOSTAS: It's just a few questions,**

:49:11 your Honor, about whether someone from his perspective, an
:49:11 entrepreneur in a small company was evaluating whether a
:49:11 product could have obtained FDA approval and deciding about
:49:11 whether they had to make changes to that product. In order
:49:11 to do so, you know, he's going to offer the opinion that
:49:11 that was a reasonable decision that was made by the
:49:11 individuals at Salmedix based on his experience, and that
:49:11 Treanda's inventions, which claim formulations and important
:49:11 improvements, in his opinion, really led to the
:49:11 approvability of that, of a product with bendamustine.
:49:11 THE COURT: Okay. There's a fine line here,
:49:11 counsel, that I think that statement does not cross. Go
:49:11 ahead.
:49:11 MR. DZWONCZYK: My objection would be if he's
:49:12 going to give an opinion as to why Ribomustin as such would
:49:12 not have been FDA approvable, because of its manufacturing
:49:12 conditions.
:49:12 THE COURT: That's not what he just said.
:49:12 MR. DZWONCZYK: I understand.
:49:12 THE COURT: Okay.
:49:12 MR. DZWONCZYK: But based on the expert reports
:49:12 and the deposition, I was afraid that is where this witness
:49:12 was going to go.
:49:12 THE COURT: Okay. But given -- you agree with
:49:12 me that given the framing of that question, that proffer,

:49:12 **that that is appropriate?**

:49:12 **MR. DZWONCZYK: If the witness says that, I**

:49:12 **wouldn't object.**

:49:12 **THE COURT: Okay. Is that what you want to**

:49:12 **do?**

:49:12 **MR. MITROKOSTAS: Yes.**

:49:12 **THE COURT: All right.**

:49:12 **(End of sidebar conference.)**

:49:14 **THE COURT: We'll try to rephrase, Doctor.**

:49:21 **BY MR. MITROKOSTAS:**

:49:25 Q. **Now, Dr. Glick, limiting yourself to theperspective of**

:49:28 **someone in Salmedix, from that business perspective, was it**

:49:33 **reasonable to conclude in your opinion that Ribomustin would**

:49:40 **not have been approved by the FDA?**

:49:41 A. **Very reasonable.**

:49:45 Q. **Have you formed an opinion about whether the patented**

:49:53 **inventions embodied by Treanda were important for the**

:49:57 **approvability of that product?**

:49:59 A. **Yes, I have.**

:50:00 Q. **What is your opinion?**

:50:01 A. **Without that invention, there would be no bendamustine**

:50:04 **on sale in the United States.**

:50:05 Q. **And can you explain why that's the case?**

:50:09 A. **Because the, the invention described in that patent,**

:50:17 **in the patent at hand, allowed one to prepare materials that**

met purity levels contemporary, purity levels of drug products, degradants, or substance of degradants. Importantly, the manufacturing process was consistent. It was reliable and it was scalable.

So one cannot launch a product in the United States unless you can actually supply the market in the United States, and we're quite a bit bigger than Germany and a couple other countries. So that is exceptionally important.

Q. And have you formed an opinion about whether the patented inventions embodied by Treanda were important for the commercial manufacturing of bendamustine product in the United States?

A. Yes, I have.

Q. And what is your opinion?

A. So, again, we've heard so -- so we've heard a number of problems with the formulation, or the formulation manufacturing of Ribomustin. And what Mr. Brittain was able to accomplish through his invention, Mr. Brittain and Mr. Franklin through their invention, the Salmedix team in general, was an elegant solution to a longstanding series of problems with manufacturing an unstable drug molecule that had a number of difficulties.

Q. Now, you mentioned that it was reasonable. You testified that it was reasonable to conclude that, from the

:51:40 **perspective of an entrepreneur at Salmedix, that Ribomustin**
:51:46 **wouldn't have been able to obtain approval?**
:51:48 A. **Right.**
:51:48 Q. **Can you explain that opinion, for what reasons was it**
:51:52 **reasonable to conclude that?**
:51:54 A. **So at the time of the license?**
:51:57 Q. **Correct.**
:51:57 A. **So there were no Phase 2 studies. As Dr. Kabakoff**
:52:02 **mentioned early on -- and this point is terribly**
:52:05 **important -- there were no proper clinical studies, what are**
:52:08 **called dose range finding studies. So having been in front**
:52:12 **of regulatory bodies designing such studies, in the FDA's**
:52:16 **mind, again, my experience and in my opinion, the FDA would**
:52:21 **have not taken for granted that the drug actually worked.**
:52:23 **That's why the Phase 2 studies that have been discussed were**
:52:27 **actually performed. So it would have been anecdotal**
:52:30 **evidence at best.**
:52:32 Q. **All right.**
:52:32 A. **So --**
:52:33 Q. **I'm sorry. I didn't mean to cut you off.**
:52:35 A. **No, that's fine.**
:52:36 Q. **So, Dr. Glick, did you hear Dr. Jarosz testify that**
:52:41 **Ribomustin, that the availability of Ribomustin makes the**
:52:48 **'270 patent claims ready for patenting?**
:52:50 A. **Yes, I did.**

Q. **Do you agree with him?**

A. **No, I don't.**

Q. **Why not?**

A. **Again, there was -- there was, really at that particular time there was nothing other than information regarding how to make materials to the specifications of the Fujisawa Ribomustin, and in no way, shape or form did it change how to make what was claimed in the invention.**

Q. **Thank you, Dr. Glick.**

MR. MITROKOSTAS: No further questions, your Honor.

THE COURT: All right. Cross-examination.

THE WITNESS: Your Honor?

THE COURT: Yes, sir?

THE WITNESS: May I stretch?

THE COURT: Absolutely.

THE WITNESS: My back.

THE COURT: Do you need a break?

THE WITNESS: No. I'm fine.

THE COURT: All right.

(Binders handed to the witness.)

MR. DZWONCZYK: Good afternoon, your Honor. Mike Dzwonczyk for Accord on behalf of all the defendants.

CROSS-EXAMINATION

BY MR. DZWONCZYK:

:54:23 Q. **Good afternoon, Dr. Glick.**

:54:24 A. **Good afternoon. Good to see you again.**

:54:26 Q. **Good to see you as well. Let's talk a little bit about derivation.**

:54:30 **On your direct testimony, you talked -- it was your opinion that Mr. Brittain did not derive the subject matter of claims 19 through 21 of the '270 patent from Fujisawa; is that correct?**

:54:41 A. **That's correct.**

:54:42 Q. **And I think you said that you reasoned because the documents didn't identify -- let me get that right. I think your testimony was that the documents you received from Fujisawa only enabled the production of a product to the Fujisawa specification, and not to the '270 patent claims; is that right?**

:55:02 A. **No. I actually think the exact word I used was "taught toward." I don't think I used the word "enabled."**

:55:08 Q. **Taught toward?**

:55:09 A. **Yes.**

:55:09 Q. **And then you talked -- we looked at a particular specification in your exhibit binder.**

:55:18 **Do you recall that?**

:55:18 A. **Yes.**

:55:19 Q. **All right. And I think we had your slide up where you**

:55:22 **illustrated that in all cases, the specification in the**
:55:26 **Fujisawa report was higher for the different levels than in**
:55:31 **the '270 patent.**
:55:32 **Do you remember that?**
:55:33 A. **Yes, I do.**
:55:34 Q. **And then you talked about the fact that you looked at**
:55:39 **maybe six or ten batches, I don't remember the number of**
:55:43 **batches that you looked at, and in all cases those batches**
:55:46 **had lower than the specification amounts called out in the**
:55:51 **Fujisawa specification; is that right?**
:55:53 A. **Yes.**
:55:53 Q. **And we can go through them, but you've already seen**
:55:57 **it.**
:55:58 **Did you look at any -- I didn't hear you talk**
:56:02 **about in your direct testimony any batches that you looked**
:56:05 **at where the actual amount of impurities from Fujisawa**
:56:09 **batches was at or higher than the specification amount; is**
:56:11 **that correct?**
:56:12 A. **That is correct.**
:56:12 Q. **And I think your testimony was that surely in the many**
:56:23 **years of making bendamustine, there must have been some**
:56:26 **batches over, at or over the specification requirements from**
:56:30 **Fujisawa; is that right?**
:56:31 A. **I added an important qualifier to that, but, yes.**
:56:34 Q. **Which was?**

:56:35 A. **Well, I have spent the majority of my career studying**
:56:40 **molecules like bendamustine, so DNA alkylating agents and**
:56:46 **cytotoxic agents. I have at least one of them now in the**
:56:49 **clinic. And in my opinion, based on my experience, that**
:56:52 **there would be a high probability that those existed.**
:56:56 **And so this is what, it's not like Salmedix**
:56:59 **went into Fujisawa and said, looked, I want this batch, I**
:57:03 **want this batch, I want this batch, and maybe they saw 50**
:57:06 **over ten years. They could have said, these all look this**
:57:10 **way. This is what Fujisawa selected to give to Salmedix.**
:57:13 Q. **So that is your evidence of what the Fujisawa**
:57:15 **specification and documentation taught; is that right?**
:57:18 A. **The document I think speaks for itself.**
:57:22 Q. **The document speaks for itself.**
:57:23 **And what Mr. Brittain had in his hand were seven**
:57:27 **batches, every one of which had a total impurity level less**
:57:31 **than five percent; is that right?**
:57:32 A. **Absolutely.**
:57:33 Q. **And every one of them had its own impurity level less**
:57:36 **than four percent?**
:57:37 A. **Absolutely.**
:57:38 Q. **And the four percent is the level that's claimed in**
:57:39 **the '270 patent; right?**
:57:41 A. **Absolutely.**
:57:42 Q. **Claim 7 and 19 through 21 of the '270 patent don't**

recite TBA anywhere in them; is that correct?
A. I believe you're correct.
Q. And they don't recite mannitol ratio; is that correct?
A. I believe you're correct.
Q. They don't recite a vial size, do they?
A. No, they do not.
Q. They're not methods of manufacturing, are they?
A. No.
Q. None of those claims, 7 and 19 through 21, talk about a formulation for a composition, do they, in the context of formulation ingredients?
A. No.
Q. The robust and reliable manufacturing methods that we've heard Mr. Brittain talk about and which you alluded to, are they anywhere claimed in the '270 patent?
A. No, they are not.
Q. On your direct testimony, you talked about the compositions of Claims 19 through 21 not being derived from Fujisawa because the levels of degradants were lower in respect of those claims than were shown in the Fujisawa documents; is that right?
A. I would have to look. I don't think I stated it exactly that way, so I'm not a hundred percent certain.
Q. Now, going back for a second to the seven lots in the

:59:25 **Fujisawa document on which the specification, in other**
:59:32 **words, the facing, page, did those seven lots also report on**
:59:34 **the amount of BM1EE in each of those lots?**
:59:38 A. **I believe they did.**
:59:39 Q. **And in every instance the lots had, the individual**
:59:42 **lots had less than 0.5 percent BM1EE; is that correct?**
:59:46 A. **I believe you're correct.**
:59:47 Q. **And that's the amount that's claimed in the '270**
:59:51 **patent claims, in Claim 21?**
:59:55 A. **I'm sorry?**
:59:55 Q. **I'm sorry. Claim 19.**
:59:56 A. **What number?**
:59:58 Q. **Claim 19.**
:59:58 A. **No. What number did you use?**
:59:59 Q. **0.5 percent?**
:00:01 A. **Yes, that is correct.**
:00:02 Q. **The Fujisawa specification allows for the manufacture**
:00:15 **of Ribomustin batches with zero impurities; is that**
:00:18 **correct?**
:00:18 A. **Scientifically, no. I have never in my -- while that**
:00:31 **may be on the four corners of the paper as a possibility,**
:00:34 **the probability of that occurring would be -- it just**
:00:38 **doesn't happen unless they're saying it's zero.**
:00:12 Q. **Is it your view that if a batch were made according to**
:00:20 **the Fujisawa specification, method of manufacture, and was**

reported to have zero impurities, that would be an out-of-spec batch?

A. No. It would mean to me that if they used a more sensitive technique they would find the impurities.

MR. DZWONCZYK: One second.

Can I have PDX-7-3.

BY MR. DZWONCZYK:

Q. Dr. Glick, you testified in the third bullet at the bottom that the claimed invention was essential to FDA approval of Treanda. Correct?

A. Correct.

Q. You are aware that Treanda 25 milligrams was approved in 2009. Right?

A. I don't recall when it was approved.

Q. Does the time frame of 2009 approximately ring a bell?

A. I will take it as a given.

Q. You are aware that the '270 patent issued in July of 2014. Right? And you can refer to JTX-1, if you would like.

A. Yes.

Q. So the '270 patent wasn't around when Treanda was approved. Correct?

A. It was pending.

Q. But it hadn't issued as a patent?

A. It was pending. That's correct.

:01:57 Q. **And you are talking about the claimed invention here.**
:02:00 **Let's skip to the '190 patent.**
:02:02 **Any of the patents, did any of the asserted**
:02:04 **patents for which you assert there are secondary**
:02:06 **considerations of nonobviousness, did they exist as an**
:02:10 **issued patent in 2009 when Treanda was approved?**
:02:13 A. **I would have to go back to all the patents. I just**
:02:16 **don't keep those dates committed to memory.**
:02:18 Q. **The FDA never stated in their NDA -- in their approval**
:02:28 **letter that their approval of Treanda was based on anything**
:02:33 **in the claims of the asserted patents?**
:02:36 A. **I would need to pull up the approval letter to know**
:02:39 **for certain what was said again. I don't commit that to**
:02:42 **memory.**
:02:42 Q. **I am just trying to get, explore the basis of your**
:02:45 **testimony that the claimed invention was essential to FDA**
:02:47 **approval. I am wondering if you saw something from FDA that**
:02:50 **told you that.**
:02:50 A. **No. I saw something from Fujisawa that told me that.**
:02:53 Q. **You mentioned a minute ago that the applications for**
:03:02 **the patents that are being litigated in this lawsuit were**
:03:05 **pending in 2009 when Treanda was approved. Is that your**
:03:08 **understanding?**
:03:10 A. **I don't know the filing date. But I assume they were**
:03:14 **pending at that point. I would have to again look to see, I**

:03:18 **would like to have all the dates lined up if we are going to**
:03:20 **talk about dates.**
:03:22 Q. **Do you know whether Cephalon ever submitted those**
:03:25 **patent applications or the pending claims to the FDA in the**
:03:29 **FDA approval process?**
:03:30 A. **I have no knowledge.**
:03:31 Q. **In the portions of the NDA you have reviewed, you**
:03:35 **didn't see any of the pending claims or pending applications**
:03:39 **as part of the dossier. Correct?**
:03:42 A. **Well, I haven't seen the specific claims as written in**
:03:46 **the patent. Certainly, the inventions, since they are not**
:03:49 **in the patent, are there.**
:03:51 Q. **Just to wrap this up, you, yourself, never spoke to**
:03:55 **anyone at the FDA who told you that Treanda was approved**
:03:59 **based on the claimed invention in these patents. Correct?**
:04:02 A. **That's correct.**
:04:05 Q. **Now, in your experience, it's not required that a**
:04:08 **proposed drug, that is the subject of an NDA, be patented in**
:04:14 **order to receive FDA approval. Right?**
:04:16 A. **That's correct.**
:04:16 Q. **You would agree with me that there are a number of**
:04:20 **FDA-approved drugs that are in fact not patented?**
:04:23 A. **I would need to look specifically. I don't want to**
:04:28 **agree either way. It may very well be that all of them are**
:04:31 **patented. But it's certainly not something that's**

:04:34 **necessarily part of the review process.**

:04:36 Q. **Referring for a moment to the license agreement that**

:04:49 **you spoke about in your direct testimony, I think you gave**

:04:52 **an opinion in your view that the cost plus 15 percent may**

:04:57 **have represented a reimbursement for the cost of goods sold.**

:05:01 **Is that approximately what your testimony was?**

:05:03 A. **Yes. That is my opinion.**

:05:05 Q. **Well, if the cost of goods sold was the cost referred**

:05:08 **to in the license agreement, the 15 percent was over and**

:05:12 **above that. Correct?**

:05:13 A. **My understanding, the 15 percent is for shipping and**

:05:17 **handling. So, yes.**

:05:19 Q. **But you don't know that from the license agreement.**

:05:21 **Right?**

:05:23 A. **Well, I sort of do, because I looked up FCA.**

:05:27 Q. **Now, you are aware, either from your review of the**

:05:37 **documents or from having heard testimony in court this week,**

:05:41 **that pursuant to the agreement, some 7000 vials of material**

:05:46 **were transferred to the U.S. Is that correct?**

:05:50 A. **Yes.**

:05:50 Q. **And I don't know if you were in the courtroom for the**

:05:55 **testimony of some of the other witnesses, but did you hear**

:05:58 **that the vials, they were small brown amber vials that were**

:06:02 **transferred?**

:06:04 A. **I don't recall if they were small -- hearing those**

:06:06 **exact words. But I will -- I believe they probab0ly were**
:06:12 **small brown vials.**
:06:13 Q. **The vials, did you hear testimony to the effect that**
:06:15 **the vials were unlabeled when they were received into the**
:06:18 **United States?**
:06:18 A. **That's correct.**
:06:18 Q. **And so they couldn't have said for experimental use**
:06:23 **only when they were received. Correct?**
:06:26 A. **They didn't say anything. They were unlabeled.**
:06:28 Q. **They were unlabeled, right.**
:06:40 **You spoke a little bit about the pharmaceutical**
:06:42 **compositions of Table 3 in the '270 patent. It was your**
:06:47 **opinion that the lots in -- I am sorry, 13 of the '270**
:06:54 **patent were not pharmaceutical compositions. Do you recall**
:06:56 **that?**
:06:57 A. **The lots, once -- yes, they do. Once they are**
:07:00 **dissolved in methanol, they are not pharmaceutical**
:07:03 **compositions according to the Court's claim construction of**
:07:06 **pharmaceutical composition.**
:07:06 Q. **Now, you don't dispute the actual values reported in**
:07:11 **Table 13, do you?**
:07:16 A. **That there are numbers?**
:07:18 Q. **I beg your pardon?**
:07:19 A. **That there are specific numbers that are stated in**
:07:23 **Table 13.**

:07:23 Q. **No. You are not challenging the values that are**
:07:26 **given. You accepted the impurity measurements of each of**
:07:28 **the recited impurities at face value. Is that correct?**
:07:31 A. **Well, I sort of do, actually, because, you know, we**
:07:35 **have to contextualize what we are talking about. If one is**
:07:38 **trying to understand levels of degradants as it relates to**
:07:42 **how this product is to be used, the data in Table 13 bear**
:07:46 **absolutely no relationship to that, because it was dissolved**
:07:49 **in methanol. If it was dissolved in sterile water for**
:07:52 **injection, that would be a different story.**
:07:53 Q. **It is not your testimony that the Ribomustin lots**
:07:55 **reported in Table 13 weren't pharmaceutical compositions.**
:07:58 **Correct?**
:08:03 A. **The lots in Table 13, as they were used in Table 13,**
:08:06 **are not pharmaceutical compositions.**
:08:09 Q. **Those same lots were used in clinical trials in**
:08:12 **patients. Correct?**
:08:13 A. **That is correct.**
:08:13 Q. **When they were used in patients, they were**
:08:15 **reconstituted in water?**
:08:16 A. **That's correct.**
:08:16 Q. **And so the lots identified in the table were**
:08:22 **manufactured and other portions of those lots were, in fact,**
:08:26 **given to patients. Correct?**
:08:28 A. **That's correct.**

:08:28 Q. **And you would agree that those were pharmaceutical**
:08:31 **compositions?**
:08:32 A. **When used in that way, they are pharmaceutical**
:08:34 **compositions, that's correct.**
:08:34 Q. **And so your testimony is based on an HPLC assay. In**
:08:41 **other words, it is your view that once dissolved in methanol**
:08:45 **and injected into an HPLC, whatever the HPLC reads is no**
:08:49 **longer a pharmaceutical composition. Correct?**
:08:52 A. **No. It is not based on the HPLC assay. It's based on**
:08:56 **the Court's claim construction.**
:08:59 Q. **I thought I heard you say on direct that the materials**
:09:03 **in Table 13 aren't pharmaceutical compositions because they**
:09:07 **are dissolved in methanol?**
:09:08 A. **That's correct.**
:09:08 Q. **And I thought I also understood you to say that the**
:09:13 **reason those couldn't be pharmaceutical compositions was**
:09:16 **because you wouldn't give methanol to a patient?**
:09:20 A. **That's correct.**
:09:20 Q. **But you don't disagree with me that the Ribomustin**
:09:26 **used for the tests, reported in Table 13, were**
:09:30 **pharmaceutical compositions otherwise given to patients?**
:09:32 A. **The dry powder that entered the test before the test**
:09:36 **was performed was a pharmaceutical composition.**
:09:38 Q. **So it's only when you take it up in methanol for the**
:09:42 **purpose of conducting a test that you are saying it's not a**

:09:46 **pharmaceutical composition?**
:09:48 A. **While your statement is correct, it's important to**
:09:52 **contextualize that in order -- because it was dissolved in**
:09:56 **methanol and there was no hydrolysis going on and the full**
:10:00 **solubility of all the degradants and all the materials has**
:10:03 **not been established in methanol, that one cannot draw any**
:10:07 **inferences regarding the true levels of degradants in that**
:10:11 **assay. That's why that assay was not used for that purpose.**
:10:14 Q. **According to your testimony, one can never know the**
:10:18 **actual amounts of degradants in a dry powder cake form of**
:10:22 **Ribomustin. Is that correct?**
:10:23 A. **No. That was not my testimony.**
:10:24 Q. **Well, if one dissolves lyophilized -- Ribomustin in**
:10:32 **methanol and injects the sample into HPLC, one obtains the**
:10:39 **degradant levels in that sample. Right?**
:10:40 A. **Can you repeat the question?**
:10:41 Q. **If someone dissolves Ribomustin, such as the lots in**
:10:45 **Table 13, in methanol and injects that dissolved compound**
:10:49 **into an HPLC, one obtains the degradants present in the**
:10:55 **Ribomustin sample. Correct?**
:10:57 A. **Possibly.**
:10:58 Q. **Are you aware of a circumstance under which it**
:11:00 **doesn't?**
:11:01 A. **There is no data -- in order to accurately answer your**
:11:04 **question, other experiments would have to be conducted.**

:11:07 Q. **Did you hear testimony this morning, a conversation**
:11:11 **between Dr. Jarosz and Mr. Ware, that the one particular lot**
:11:16 **of Table 13 with an HP1 level of .93 looks like it was a**
:11:23 **little over two years old?**
:11:25 A. **I believe I recall that, yes.**
:11:26 Q. **It was manufactured some two years before the HPLC**
:11:33 **measurement was actually taken. Do you recall that?**
:11:34 A. **I do.**
:11:35 Q. **And the degradant level for HP1 was .93. Do you**
:11:40 **remember that?**
:11:40 A. **Yes, I do.**
:11:41 Q. **Do you have an expectation one way or the other if**
:11:44 **that HPLC measurement was actually made on that lot during**
:11:51 **what would have been the shelf life of that product,**
:11:53 **wouldn't the degradation -- would the degradant quantity of**
:11:56 **HP1 be lower?**
:12:00 A. **It would be impossible to say just from the -- without**
:12:05 **reviewing every piece of information, because conditions**
:12:09 **really matter, and when we started the lot, it was at 1.6,**
:12:14 **if I recall the table correctly, going down to 0.93, and**
:12:18 **then looking to see how both were measured. It's very hard,**
:12:22 **because while we are talking about important differences,**
:12:26 **the differences themselves are in magnitude small.**
:12:28 **It's a tough question to really answer.**
:12:31 Q. **Thinking back for a second, Dr. Glick, to Claims 19**

:12:54 **and 21 of the '270 patent, they say nothing about the**
:12:57 **solvent system used for reconstitution, do they?**
:13:03 A. **Can we pull up the --**
:13:05 Q. **Can we have Claims 19 through 21 of the '270 patent,**
:13:09 **JTX-5.**
:13:38 A. **Okay.**
:14:03 Q. **Claims 19 to 21 don't say anything about the solvent**
:14:10 **that is used to measure the degradant that's reported in**
:14:14 **these claims; is that right?**
:14:15 A. **So while there's no specific liquid or solvent**
:14:18 **mentioned in those specific claims, I think it's implicit**
:14:23 **for a person of ordinary skill in the art to know that**
:14:25 **the solvent that's going to be -- that one would, since**
:14:29 **these are treatment claims use, is one that could be**
:14:31 **administered --**
:14:32 Q. **Dr. Glick, you can do that with your counsel on**
:14:34 **redirect. I just asked you if there's any solvent recited**
:14:37 **in these claims at all?**
:14:38 A. **I apologize, but I'm answering this as to how I**
:14:42 **would -- as a person of skill in the art, when I read this,**
:14:45 **I think it would be implicit. I would take that for**
:14:47 **granted. But you are correct, there's not -- there's no**
:14:50 **specific solvent listed.**
:14:52 Q. **And there's no limitation in these claims directed to**
:14:55 **product stability; is that right?**

:14:57 A. **Again, in my reading of Claim 19, there are --**
:15:09 **there's something implicit there, but it is not explicitly**
:15:14 **stated.**
:15:15 Q. **Nothing in these claims talk about the amount of**
:15:18 **mannitol; is that correct?**
:15:19 A. **That's correct.**
:15:20 Q. **Nothing in these claims talks about the amount of**
:15:23 **bendamustine; is that correct?**
:15:23 A. **That's correct.**
:15:26 Q. **And, again, the claims are recited on the use of TBA;**
:15:31 **right?**
:15:32 A. **That's correct.**
:15:33 Q. **You talked about the development of an HPLC method**
:15:46 **based on the material that was received from Fujisawa; is**
:15:50 **that correct?**
:15:50 A. **Yes.**
:15:51 Q. **And, in fact, the HPLC method was an optimized process**
:15:56 **based on an earlier HPLC method in order to better separate**
:16:01 **the bendamustine degradants; is that correct?**
:16:04 A. **I believe it is a different protocol. I have not**
:16:09 **looked at them side by side, but I know that it is a process**
:16:13 **that improves, that what we're looking at is something that**
:16:16 **gives you better resolution.**
:16:17 Q. **It better resolves two of the impurities that were**
:16:20 **otherwise poorly resolved by a different procedure; is that**

correct?
A. Yes. I don't remember which impurities off the top of my head.
Q. And optimizing or modifying an HPLC method, isn't that what an analytical chemist does every day?
A. Analytical, some analytical chemists spend their days looking at HPLCs.
Q. Well, if the an HPLC afforded poor resolution of two compounds, isn't it quite routine to vary components or features of the HPLC process to resolve the unresolved compounds?
A. Well, and I spent 25 years doing, probably longer doing HPLC, and what I can say is that while one might want to do that, it again is not a foregone conclusion that one could develop a separation method that would, in fact, do it. I spent many, many unsuccessful late nights trying.
Q. In your view, review of the documents pertaining to Salmedix, is it your understanding that Salmedix back in the 2003 time frame was a venture funded company?
A. I believe venture capital was used for the initial financing of the company, that's correct.
Q. Salmedix was in the business of trying to bring, develop drugs and bring them to market; is that correct?
A. I believe that's an accurate statement.

Q. **And regardless of the source, they were funded to do that very thing, weren't they?**

A. **You know, I would want to see their business plan or their, you know, their overall sort of corporate shield. But, yeah, that would be generally correct.**

Q. **Well, based on your experience, wouldn't the development work being done by Salmedix itself be a commercial venture?**

A. **No.**

Q. **I'm not talking about the sale of the product, but were the employees, the 20-some employees of Salmedix paid for what they did?**

A. **I would hope so.**

Q. **And for the period of time during which Salmedix was developing this product, they were making a profit for the work that they did, weren't they?**

A. **I'm sorry. Can you please repeat it?**

Q. **I will withdraw the question.**

MR. DZWONCZYK: Give me a second, your Honor.

THE COURT: It's withdrawn.

(Pause.)

BY MR. DZWONCZYK:

Q. **I just have a couple more questions, Dr. Glick.**

You are aware that -- you're aware that Treanda is approved for use in the treatment of CLL, or chronic

lymphocytic lymphoma?
A. Leukemia, I believe, but I -- yes, it's approved for hematological uses. That's correct, yes.
Q. And you're also aware that Cephalon has received an orphan drug designation for the treatment of CLL?
A. I would want to see it again to make sure that I had seen that, but I'm not sure that's a document that I, I recall reviewing.
Q. Would you take a look at DTX-161 in the binder that we handed you.
MR. DZWONCZYK: Mr. Vaughn, would you blow up the middle paragraph of DTX-161.
BY MR. DZWONCZYK:
Q. Referring you to the paragraph on the screen, Dr. Glick, do you see that the FDA approved Cephalon's request that Treanda be indicated for the treatment of CLL on an orphan, in an orphan status?
A. Yes, I do.
Q. The last sentence of the paragraph says, "Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated."
Do you see that?
A. I do.
Q. And so the FDA's approval, I'm sorry, designation of orphan status was not based on the formulation of Treanda,

it was based solely on bendamustine hydrochloride; is that correct?

A. That's what that document says, correct.

Q. And in order to get its approval for CLL, are you aware that the NDA relies on a single study based on comparison of Ribomustin with a different drug?

A. As I mentioned, I didn't review this. I want to know more about this NDA, this application and its relation to the documents that I received or reviewed to make sure that we're talking apples to apples.

Q. Would you take a look at PTX-372 in the binder that we've provided to you.

A. Thank you.

Q. On the second page of the document is a subheading called "Treanda in CLL," and I would direct your attention to that portion.

Do you see that?

A. I'm sorry. Yes. I'm just reading it now.

Q. Oh, okay. Please do.

In this press release by Cephalon, it states the Treanda NDA for the treatment of patients with CLL is based on a large, international multi-center Phase 3 clinical trial that evaluated the safety and efficacy of bendamustine hydrochloride, the active ingredient in Treanda, compared to chlorambucil in patients who were not previously treated for

:23:04 **the disease.**

:23:04 **Do you see that?**

:23:05 A. **Yes, I do.**

:23:06 Q. **And that study they're referring to is talking about**

:23:09 **bendamustine, the active ingredient in Treanda, rather than**

:23:12 **the Treanda formulation; is that correct?**

:23:14 A. **That's what this paragraph speaks to, yes.**

:23:16 Q. **And does this refresh any recollection you have that**

:23:19 **the CLL indication was based on bendamustine hydrochloride**

:23:23 **and Ribomustin rather than the Treanda formulation?**

:23:26 A. **None whatsoever.**

:23:27 Q. **Okay.**

:23:33 **MR. DZWONCZYK: I have no further questions.**

:23:35 **THE COURT: All right.**

:23:37 **MR. MITROKOSTAS: No redirect, your Honor.**

:23:38 **THE COURT: Thank your, Doctor. You are**

:23:39 **excused.**

:23:40 **(Witness excused.)**

:23:43 **THE COURT: All right. Where are we?**

:23:47 **MR. MITROKOSTAS: If we could have one moment,**

:23:49 **your Honor.**

:23:49 **(Pause while counsel conferred.)**

:24:01 **MR. WIESEN: Your Honor, could we request a**

:24:02 **short recess so we can figure out what we want to do with**

:24:05 **the next witness?**

:24:05 **THE COURT: The next witness, direct would be approximately how long?**

:24:13 **MR. WIESEN: We need to determine what subjects it would cover, if any, so if you could give us five minutes?**

:24:19 **THE COURT: Is there a witness you think you can present in the next 55 minutes that can be directed and crossed?**

:24:26 **MR. WIESEN: It's possible. Our next witness will be short, if we call him at all.**

:24:29 **THE COURT: Is the witness available on Monday?**

:24:32 **MR. WIESEN: He would be available on Monday.**

:24:34 **THE COURT: We'll do it on Monday. All right. Okay? Unless it's going to cause a significant inconvenience.**

:24:40 **MR. WIESEN: No.**

:24:41 **THE COURT: All right.**

:24:47 **MR. WIESEN: Can you give me one minute to check with the witness?**

:24:50 **THE COURT: Yes. I will give you a minute.**

:24:51 **(Pause.)**

:25:18 **THE COURT: Is it a technical witness?**

:25:20 **MR. WIESEN: It is, your Honor, but if we could have a one more minute, I think we can resolve the issue.**

THE COURT: All right.

MR. WARE: I think --

THE COURT: If it wasn't a technical witness, I would be less --

MR. WIESEN: Understood. I think we've decided we're not going to call him at all, so we don't need to call him today.

THE COURT: All right.

(Pause while counsel conferred.)

MR. WARE: Your Honor, we're not going to call the witness at all.

THE COURT: All right. So then Monday, 9:00 o'clock.

MR. WIESEN: Yes, your Honor.

THE COURT: Have a good weekend, all.

MR. WIESEN: Thank you.

(Court recessed at 4:10 p.m.)